Rapid, Semi-automated Convergent Synthesis of Low Generation Triazine Dendrimers using Microwave Assisted Reactions

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General Experimental

Microwave. A CEM SP Discovery microwave was utilized for these experiments. Reactions were performed in dynamic mode wherein microwave power is modulated to maintain the set-point temperature—here either 60 ^{o}C or 95 ^{o}C.

Automated chromatography. A CombiFlash RF automatic chromatographer (Teledyne ISCO) was used for these experiments. The separations were performed using a solid loading method in a 25 g preloaded cartridge.

Compound 1. *N*-BOC-4,7,10-trioxa-1,13-tridecanediamine (4.03 g, 12.6 mmol) was added to a solution of cyanuric chloride (1.06 g, 5.72 mmol) in THF (50 mL). Afterwards DIPEA (4.38 mL, 13.2 mmol) was added dropwise. The solution was stirred for 2 minutes in order to allow reagents to mix. Then, the solution was irradiated in the microwave while stirring for 10 minutes at 60ºC using dynamic mode. The crude product was purified automatic chromatographer. The solvent system (in column volumes) used was the following: 4 CV (100% Hexanes to 100% EtoAc), 20CV(100% EtoAc) to give **1** (4.08 g, 95%) as a clear oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.67-3.45 (m, 28H, **CH$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.24 (br m, 4H, BocNHC**H$_2$**), 1.88-1.75 (m, 8H, OCH$_2$**CH$_2$**CH$_2$), 1.44 (s, 18H, C(C**H$_3$**)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.9, 168.0, 165.9 (**C$_3$N$_3$**), 156.1 (**C**O), 78.8 (**C**(CH$_3$)$_3$), 70.5 (O**CH$_2$CH$_2$**O), 70.2 (two lines, O**CH$_2$CH$_2$**O), 69.5 (**CH$_2$**CH$_2$CH$_2$O), 69.3 (CH$_2$CH$_2$**CH$_2$**O), 38.4 (CH$_2$**CH$_2$**CH$_2$O), 29.5 (**CH$_2$**CH$_2$CH$_2$O), 28.6 (NHCH$_2$**CH$_2$**CH$_2$O), 28.4 (C(**CH$_3$**)$_3$); MS (ESI-TOF) calcd for C$_{33}$H$_{62}$ClN$_7$O$_{10}$ 751.4247, found 752.4382(M + H)$^+$.

Figure S1. ^{1}H NMR Spectrum of **1**.
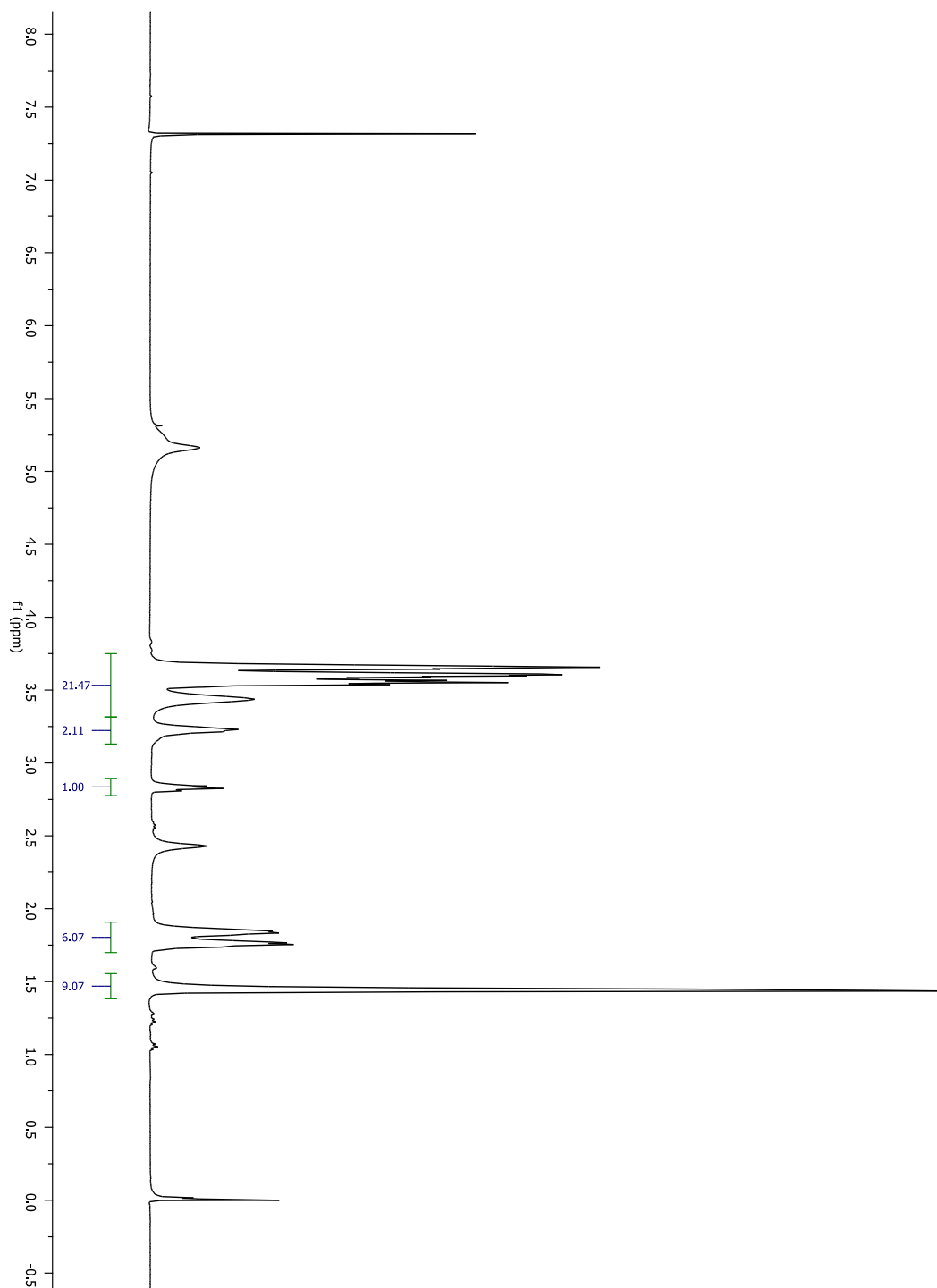
Figure S2. ^{13}C NMR Spectrum of **1**.

Figure S3. Mass Spectrum of **1**.

Sample Name: RCB-91-12colum(4)
Inj Vol: -1
Data Filename: RCB-91-12colum(4).d

Position: P1-A1
InjPosition:
ACQ Method:

Instrument Name: Instrument 1
SampleType: Sample
Comment:

User Name:
IRM Calibration Status: All Ions Missed
Acquired Time: 5/23/2013 11:49:16

×10 2 +ESI Scan (0.5982 min) Frag=175.0V RCB-91-12colum(4).d

752.4382

Counts (%) vs. Mass-to-Charge (m/z)

7

Compound 2. A solution of **1** (6.66g, 8.85 mmol) with 4,7,10-trioxa-1,13-tridecanediamine (7.8 g, 35.4 mmol) and Cs_2CO_3 (5.77g, 17.7 mmol) in 40 mL of 1,4 dioxane was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 30 minutes at 95ºC and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over MgSO4, filtered, and evaporated under vacuum. The separation was performed using a solid loading method in a 25 g preloaded cartridge. The solvent system (in column volumes) used was the following: 30CV (90:10= DCM: MeOH), 20CV (85:15= DCM: MeOH), 15CV (5:1:1% = DCM: MeOH: NH4OH) to give 5 (7.2 g, 87%) as a clear oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.63-3.34 (m, 42H, **CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.20 (m, 4H, BocNHC**H$_2$**), 2.79 (t, J = 6.6, 2H, OCH$_2$CH$_2$C**H$_2$**NH$_2$), 1.82-1.73 (m, 12H, OCH$_2$C**H$_2$**CH$_2$), 1.40 (s, 18H, C(C**H$_3$**)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.0 (**C**$_3$N$_3$), 156.2 (**C**O), 78.8 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$CH$_2$O), 70.3 (O**C**H$_2$CH$_2$O), 70.2 (two lines, O**C**H$_2$CH$_2$O), 69.5 (**C**H$_2$CH$_2$CH$_2$O), 69.3 (**C**H$_2$CH$_2$CH$_2$O), 39.5 (**C**H$_2$CH$_2$CH$_2$O), 38.5 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 32.7 (O**C**H$_2$CH$_2$CH$_2$NH$_2$), 29.7 (NH**C**H$_2$CH$_2$CH$_2$O), 28.5 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for C$_{43}$H$_{85}$N$_9$O$_{13}$ 935.6267, found 936.6724(M + H)$^+$.
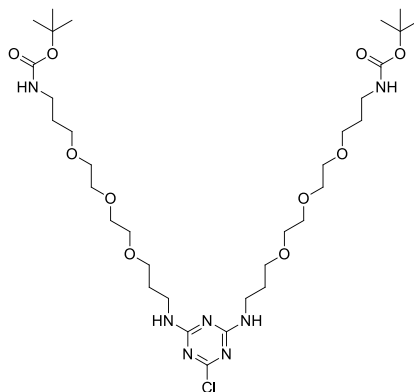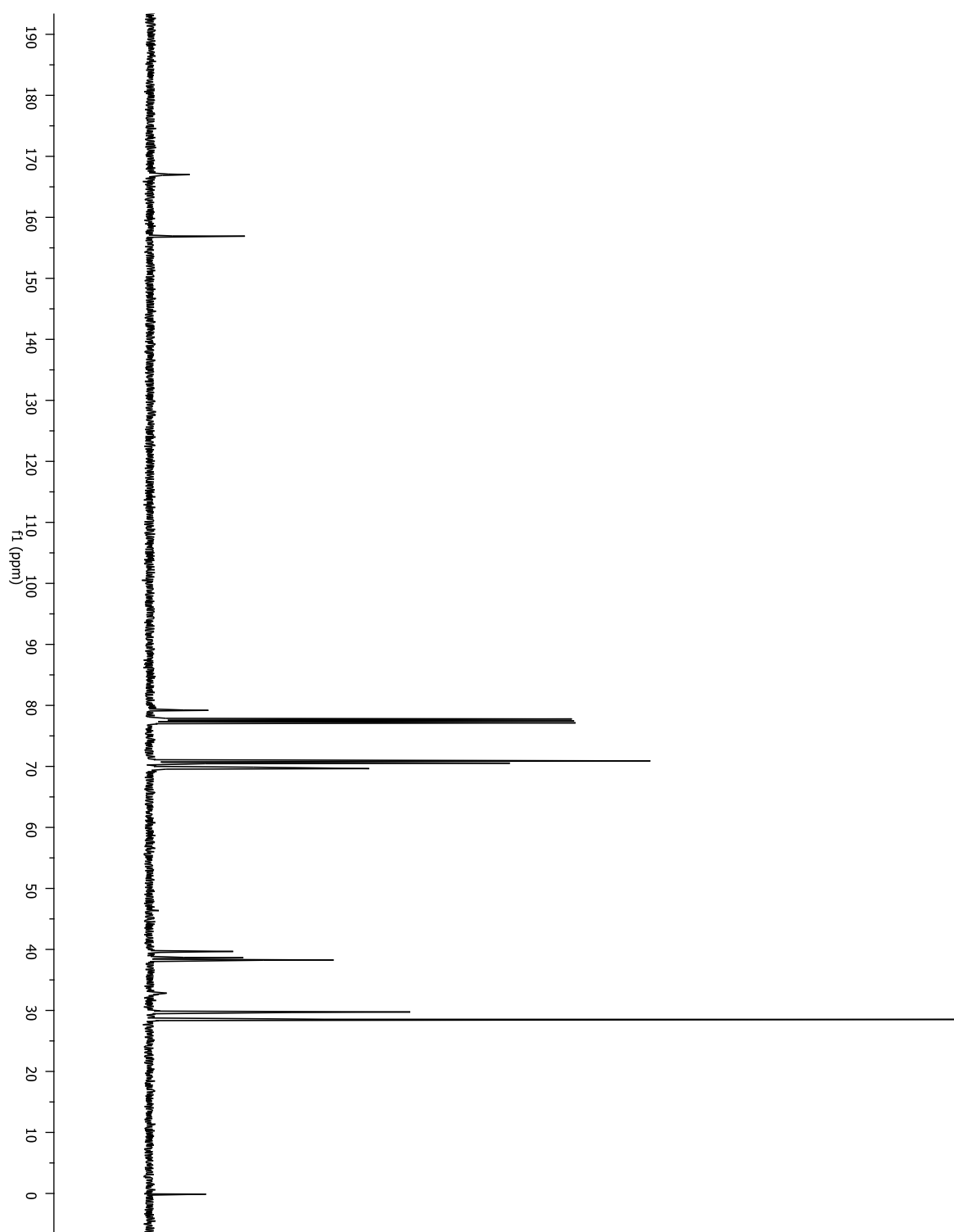
Figure S4. ^{1}H NMR Spectrum of **2**.
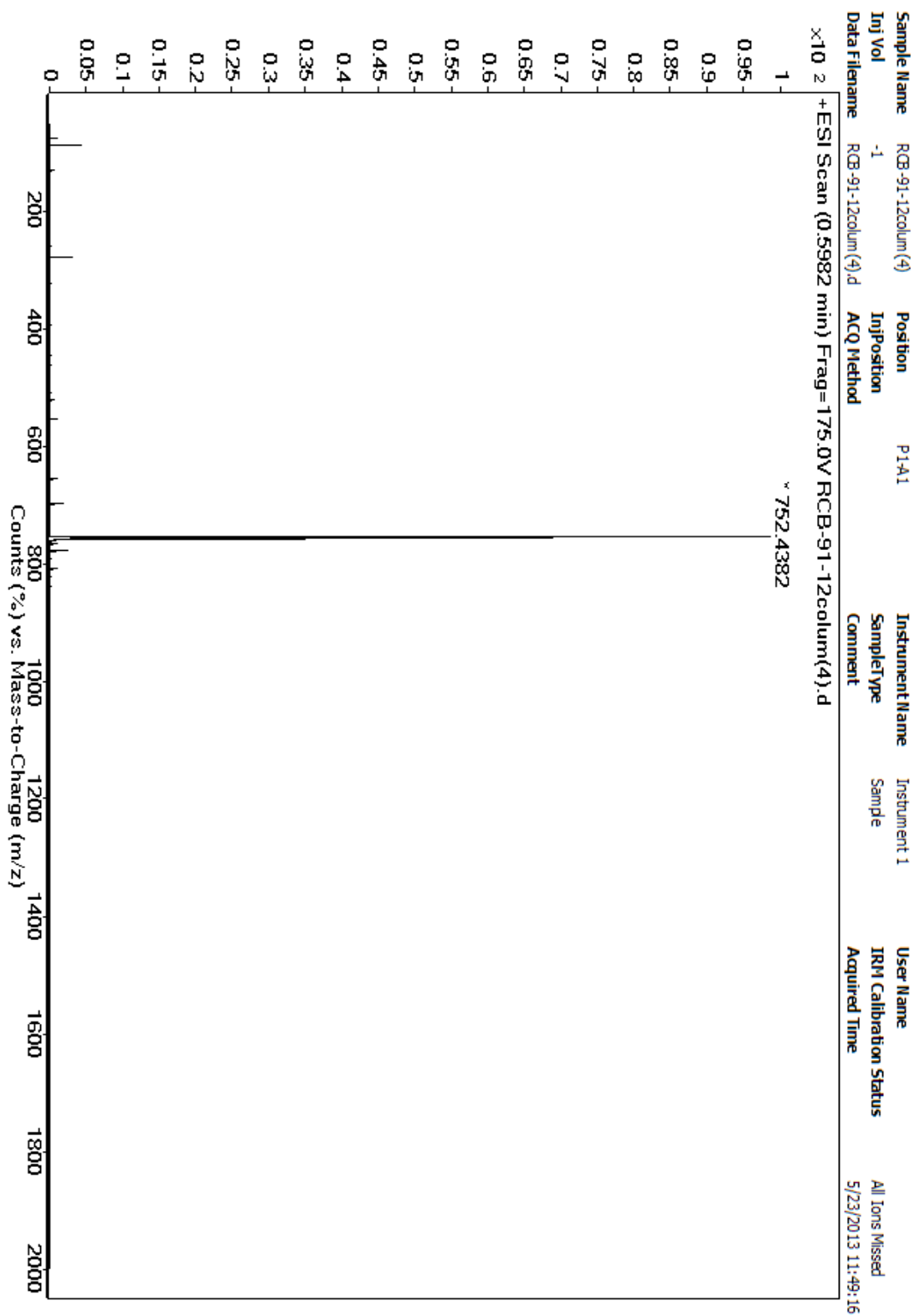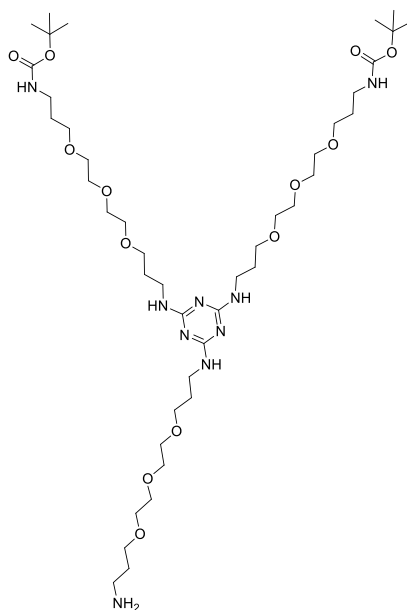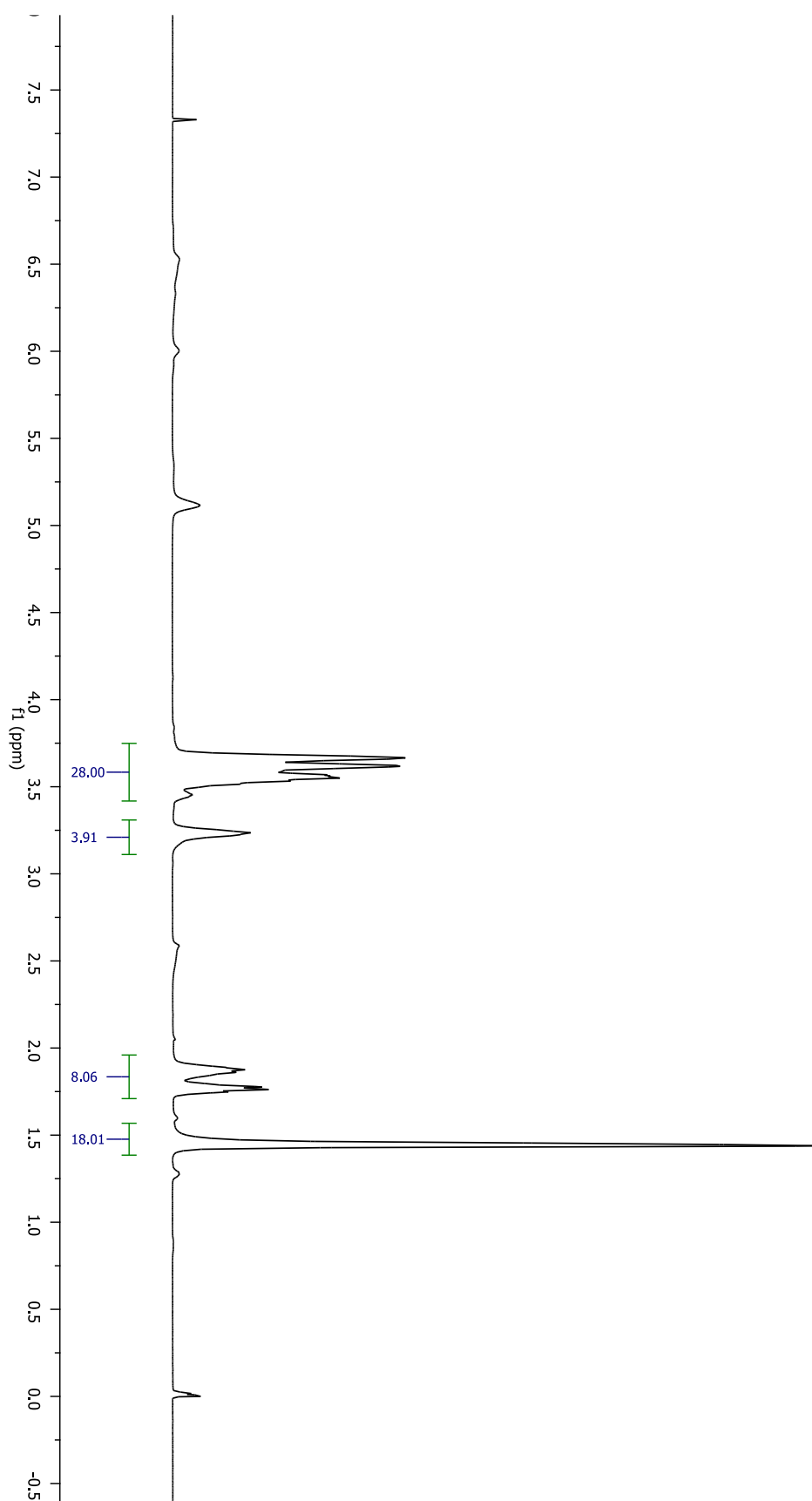
Figure S5. ^{13}C NMR Spectrum of **2**.

Figure S6. Mass Spectrum of **2**

Sample Name	premacro-AE2057	Position	P1-A1	Instrument Name	Instrument 1	User Name	
Inj Vol	-1	InjPosition		SampleType	Sample	IRM Calibration Status	All Ions Missed
Data Filename	premacro-AE2057.d	ACQ Method		Comment		Acquired Time	7/22/2013 11:01:58

×10 ² | + ESI Scan (0.6106 min) Frag=75.0V premacro-AE2057.d

468.8465

936.6706

Counts (%) vs. Mass-to-Charge (m/z)
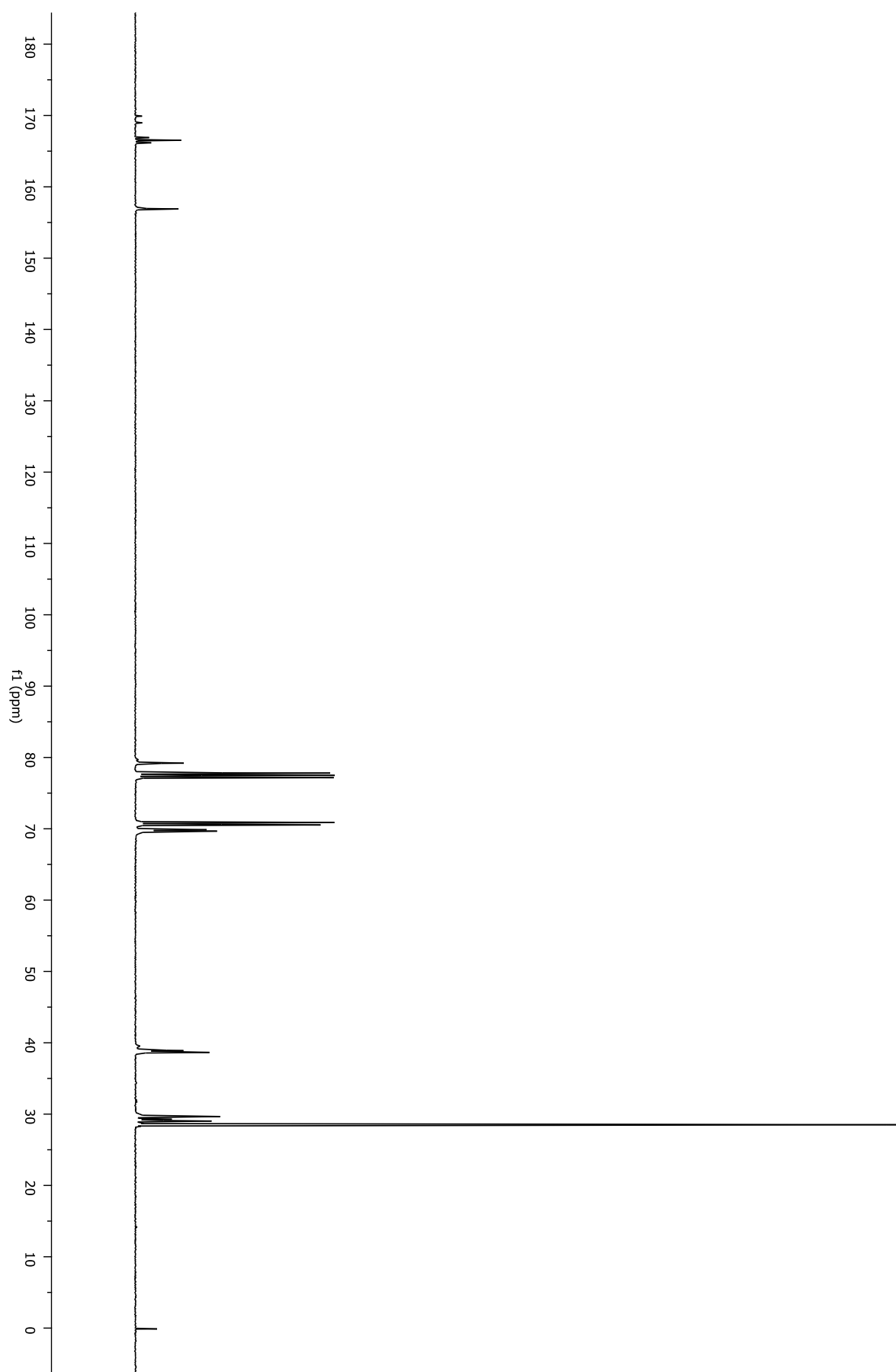
Compound 3 (macromonomer). Compound **2** (4.08 g, 4.36 mmol) was added to a solution of cyanuric chloride (0.366 g, 1.98 mmol) in THF (20 mL). Afterwards DIPEA (3.2 mL, 9.32 mmol) was added dropwise, and the solution was stirred for 2 minutes in order to allow reagents to mix. Then, the solution was irradiated in the microwave while stirring for 10 minutes at 60ºC using dynamic mode. The solvent system (in column volumes) used was the following: 1 CV (100% DCM to 95:5= DCM: MeOH), 15CV (95:5= DCM: MeOH), 10CV (90:10= DCM: MeOH), 20CV (85:15= DCM: MeOH) to give **1** (3.85g, 98%) as a clear oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.65-3.43 (m, ~~88H~~, **CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.21 (br m, 8H, BocNHC**H$_2$**), 1.83-1.70 (m, 24H, OCH$_2$C**H$_2$**CH$_2$), 1.44 (s, 36H, C(**CH$_3$**)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.9 (**C**$_3$N$_3$), 165.6 (**C**$_3$N$_3$), 156.1 (**C**O), 78.8 (**C**(CH$_3$)$_3$), 70.5 (O**C**H$_2$CH$_2$O), 70.2 (two lines, O**C**H$_2$CH$_2$O), 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 38.4 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for C$_{89}$H$_{168}$ClN$_{21}$O$_{26}$ 1982.2158, found 1984.4671 (M + H)$^+$.

Figure S7. ^{1}H NMR Spectrum of **3.**
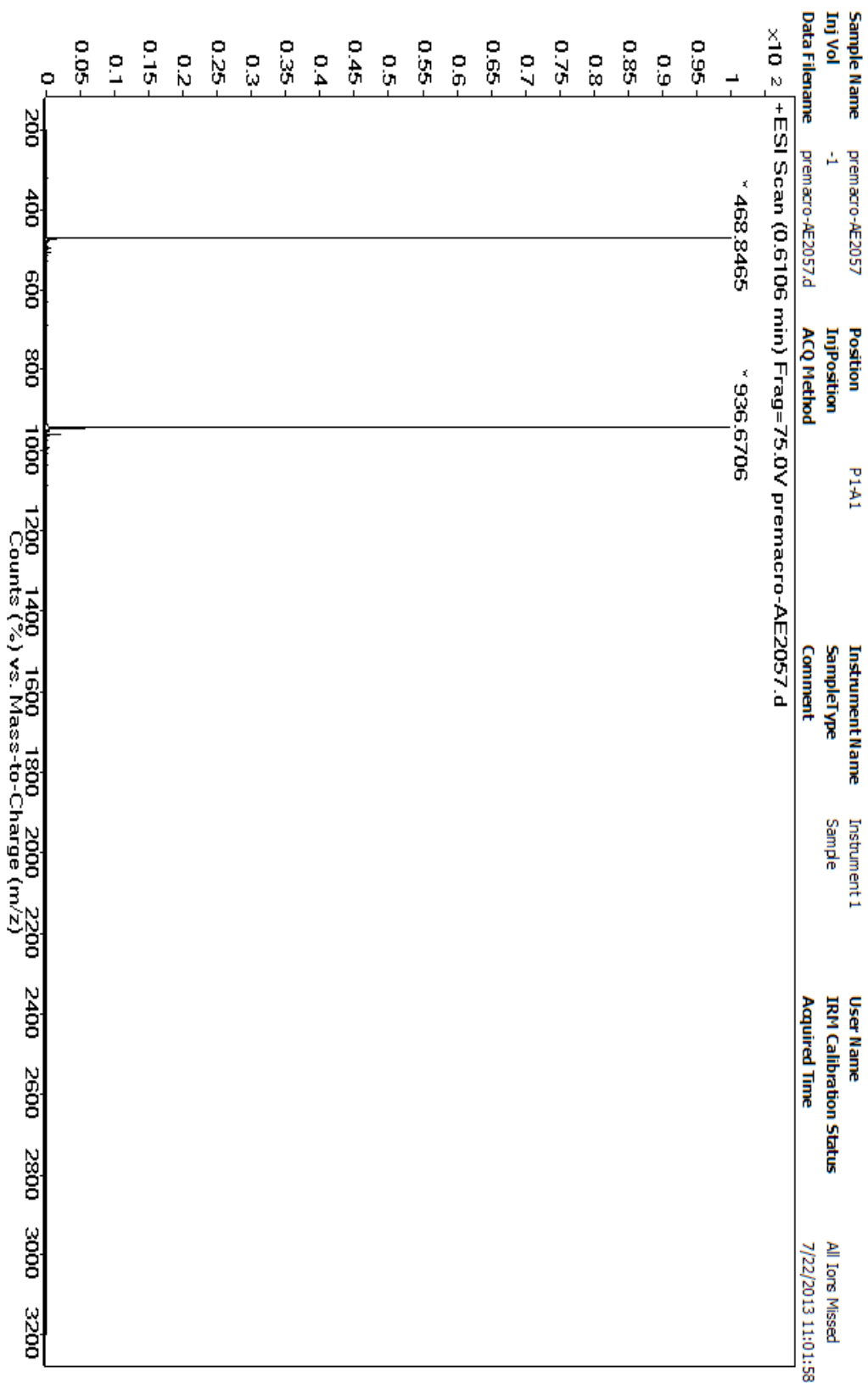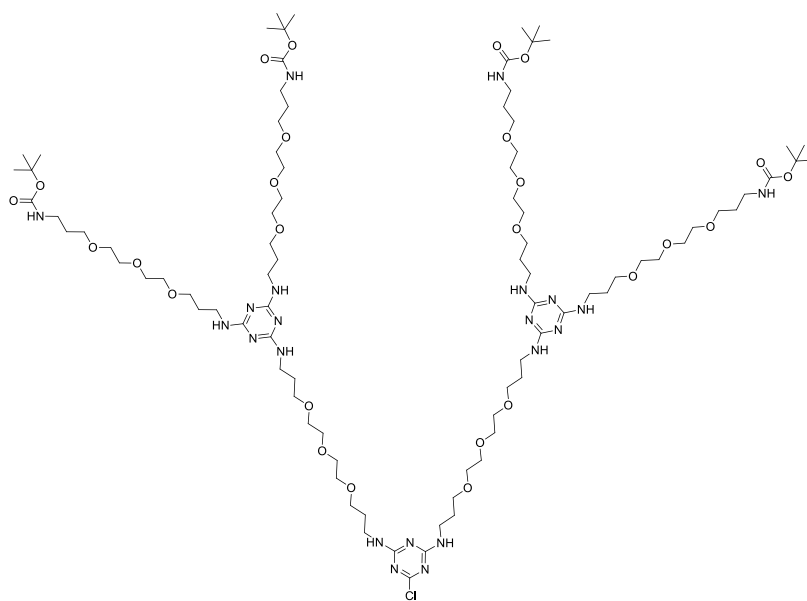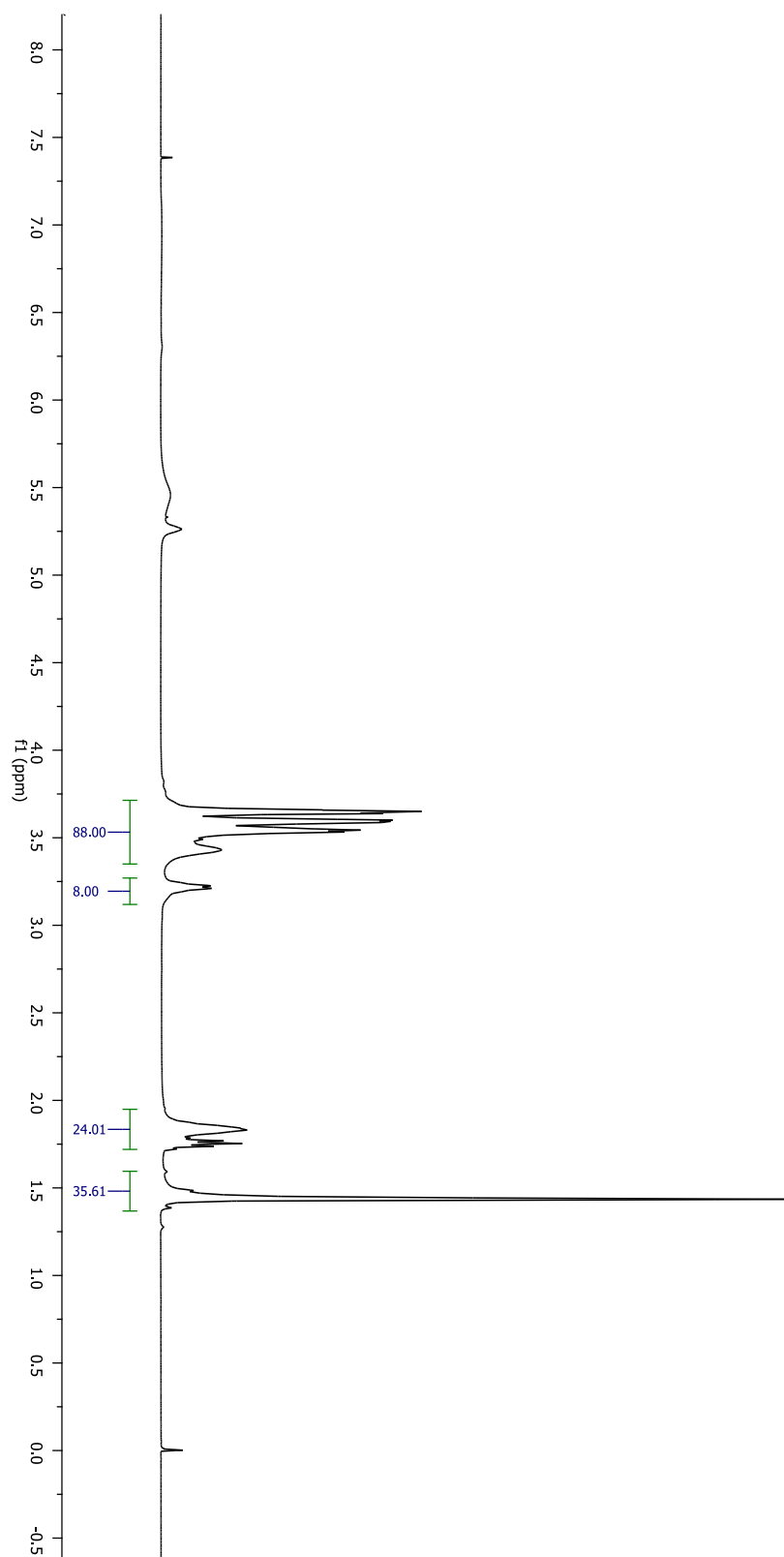
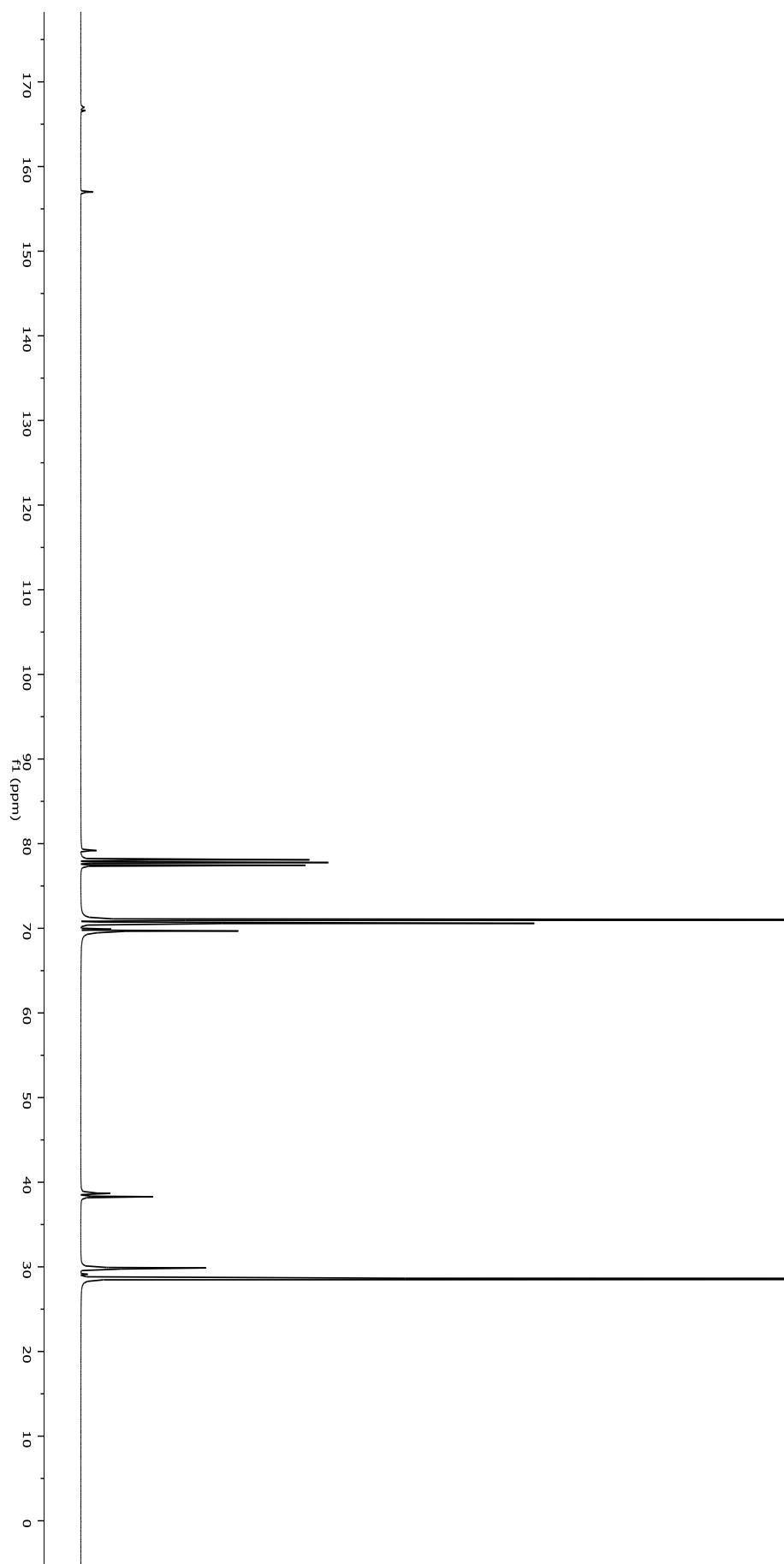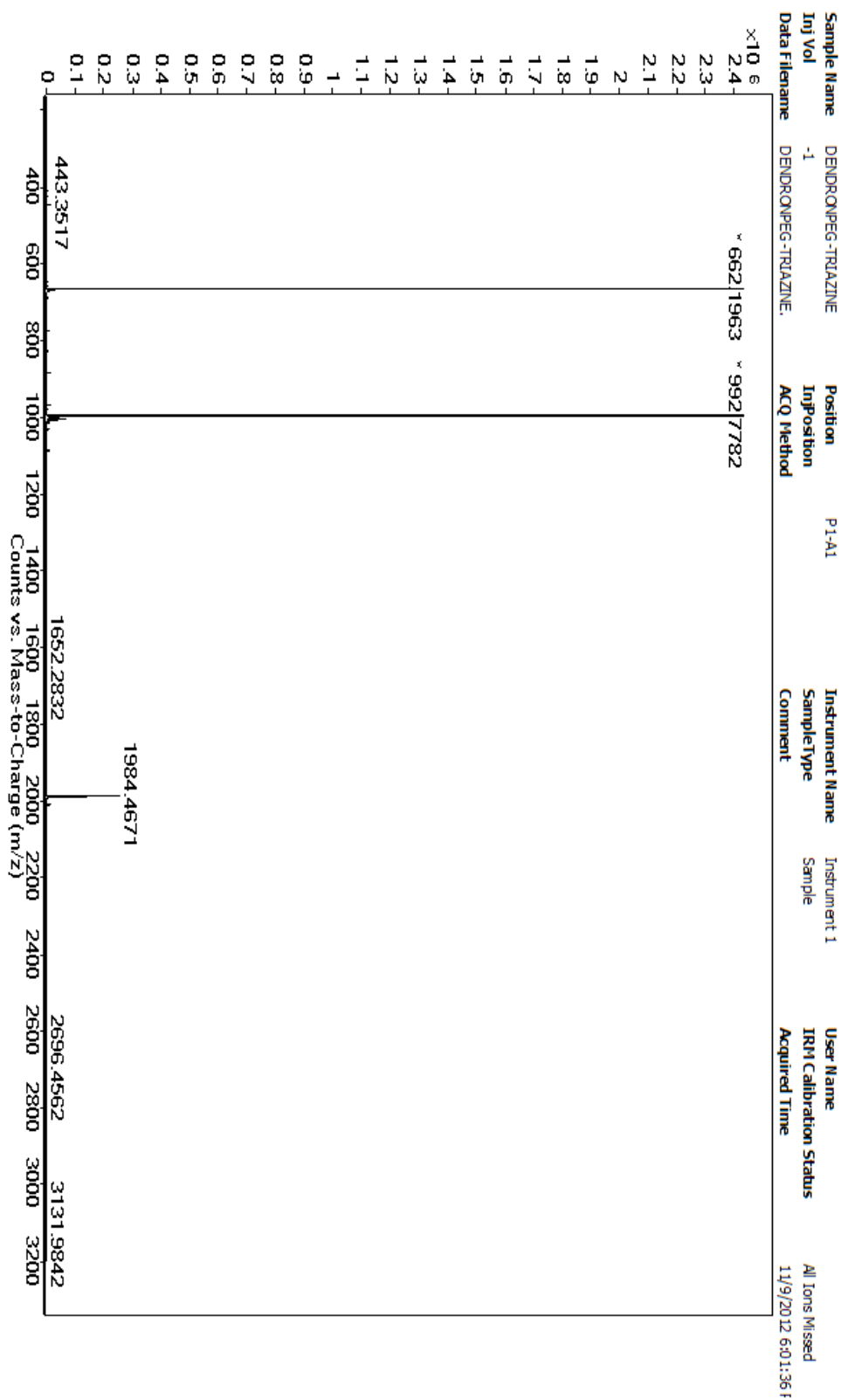Figure S8. ^{13}C NMR Spectrum of **3.**

Figure S9. Mass Spectrum of **3**. Doubly and triply charged species are observed.

Compound 4 (G1.5) A solution of **1** (2.043g, 1.03 mmol) with 4,7,10-trioxa-1,13-tridecanediamine (2.27g, 10.3 mmol) and Cs_2CO_3 (0.67g, 2.06 mmol) in 10 mL of 1,4 dioxane was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 30 minutes at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by automated chromatography. The solvent system (in column volumes) used was the following: 1CV (100% DCM), 3CV (100% DCM to 90:10= DCM: MeOH), 10CV (90:10= DCM: MeOH), 2CV (90:10= DCM: MeOH to 85:15= DCM: MeOH), 2CV (85:15= DCM: MeOH to 80:20= DCM: MeOH), 5CV (80:20= DCM: MeOH), 10CV (5:1:1% = DCM: MeOH: NH₄OH) to give **4** (1.89g, 85%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64-3.46 (m, 102H, **CH₂OCH₂CH₂OCH₂CH₂OCH₂**, C_3N_3-NHC**H₂**CH₂CH₂O), 3.21 (br m, 8H, BocNHC**H₂**), 2.0 (m, 2H, NH₂C**H₂**CH₂CH₂O) 1.84-1.73 (m, 28H, OCH₂C**H₂**CH₂), 1.43 (s, 36H, C(C**H₃**)₃); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.11 (**C**₃N₃), 157.06 (**C**O), 79.28 (**C**(CH₃)₃), 71.01 (O**C**H₂CH₂O), 70.7 (two lines, O**C**H₂**C**H₂O), 69.97 (**C**H₂**C**H₂CH₂O), 69.67 (CH₂**C**H₂**C**H₂O), 39.77 (NH₂**C**H₂CH₂CH₂O), 38.75 (**C**H₂CH₂CH₂O), 38.34 (CH₂CH₂**C**H₂O), 32.73 (NH₂CH₂**C**H₂CH₂O), 29.87 (NHCH₂**C**H₂CH₂O), 28.64 (C(**C**H₃)₃); MS (ESI-TOF) calcd for $C_{99}H_{191}N_{23}O_{29}$ 2166.4178, found 2168.4939 $(M + H)^+$.
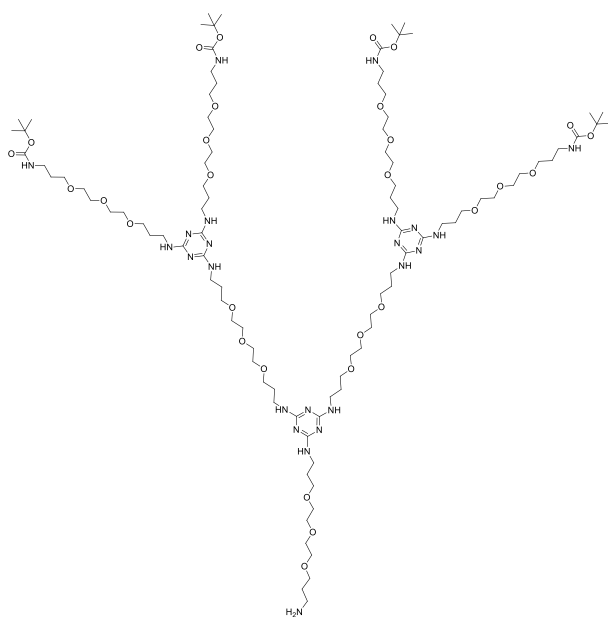
Figure S10. ^{1}H NMR Spectrum of **4**.
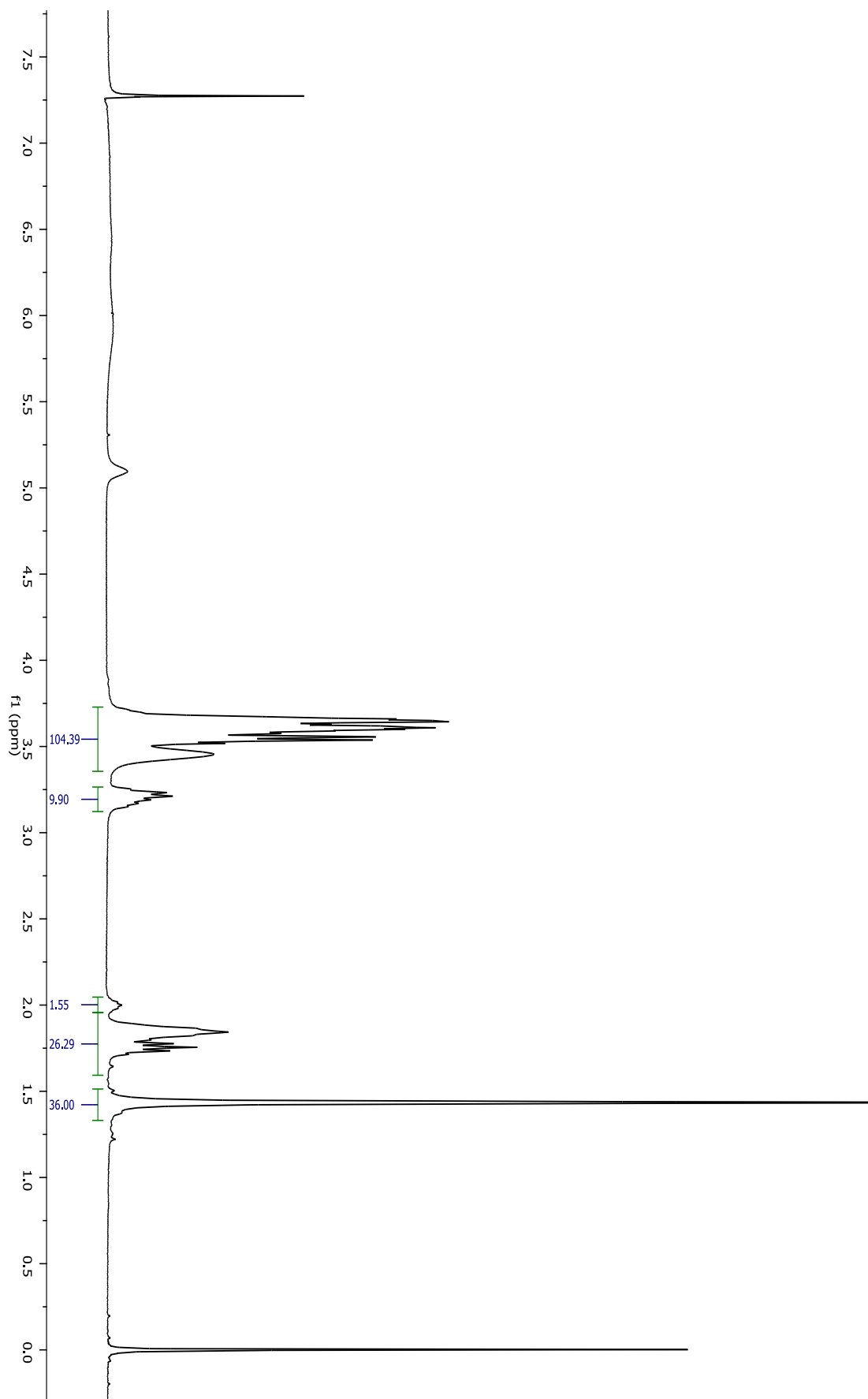
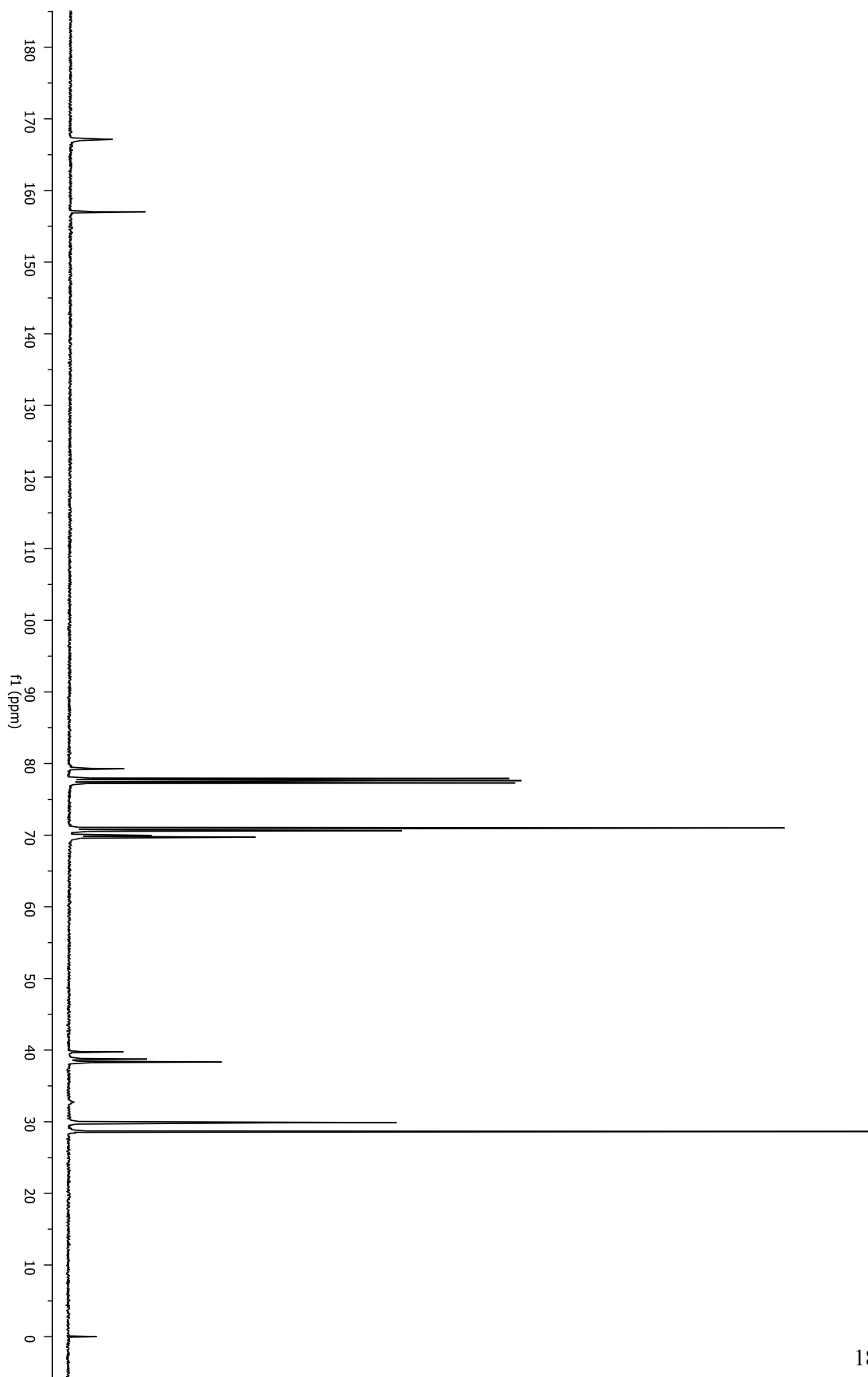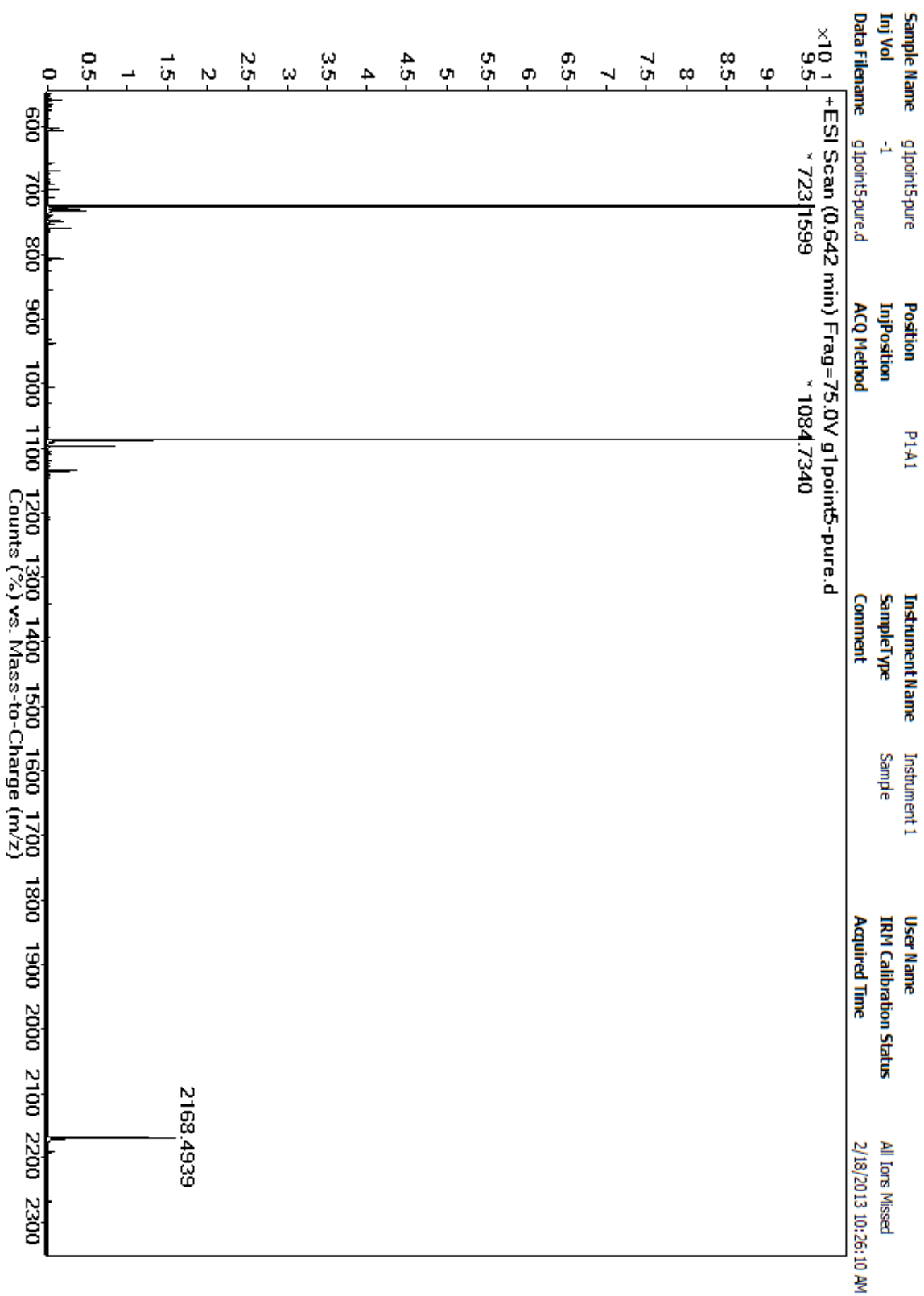Figure S11. ^{13}C NMR Spectrum of **4**.

Figure S12. Mass Spectrum of **4**.

Compound 5 (G2-C l) Compound **4** (2.95 g, 1.36 mmol) was added to a solution of cyanuric chloride (0.114 g, 0.62 mmol) in THF (6 mL). Afterwards DIPEA (0.46 mL, 2.6 mmol) was added dropwise. The solution was stirred for 2 minutes in order to allow reagents to mix. Then, the solution was irradiated in the microwave while stirring for 10 minutes at 60ºC using dynamic mode. The crude product was purified automated chromatography. The solvent system (in column volumes) used was the following: 1 CV (100% DCM to 95:5= DCM: MeOH), 15CV (95:5= DCM: MeOH), 10CV (90:10= DCM: MeOH), 5CV (85:15= DCM: MeOH), 5CV (80:20= DCM: MeOH) to give **5** (2.5g, 91%) as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.65-3.44 (m, 208H, **CH$_2$**OC**H$_2$**CH$_2$OC**H$_2$**CH$_2$OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.21 (br m, 16H, BocNHC**H$_2$**), 1.83-1.74 (m, 56H, OCH$_2$**CH$_2$**CH$_2$), 1.44 (s, 72H, C(**CH$_3$**)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.6 (**C$_3$N$_3$**), 157.02 (**C**O), 79.29 (**C**(CH$_3$)$_3$), 70.97 (O**CH$_2$CH$_2$**O), 70.64 (two lines, O**CH$_2$CH$_2$**O), 69.94 (**CH$_2$**CH$_2$CH$_2$O), 69.64 (CH$_2$CH$_2$**CH$_2$**O), 38.73 (**CH$_2$**CH$_2$CH$_2$O), 38.38(CH$_2$**CH$_2$**CH$_2$O), 29.73 (NHCH$_2$**CH$_2$**CH$_2$O), 28.6 (C(**CH$_3$**)$_3$); MS (ESI-TOF) calcd for C$_{201}$H$_{380}$ClN$_{49}$O$_{58}$ 4443.7980, found 4447.6713 (M + H)$^+$.
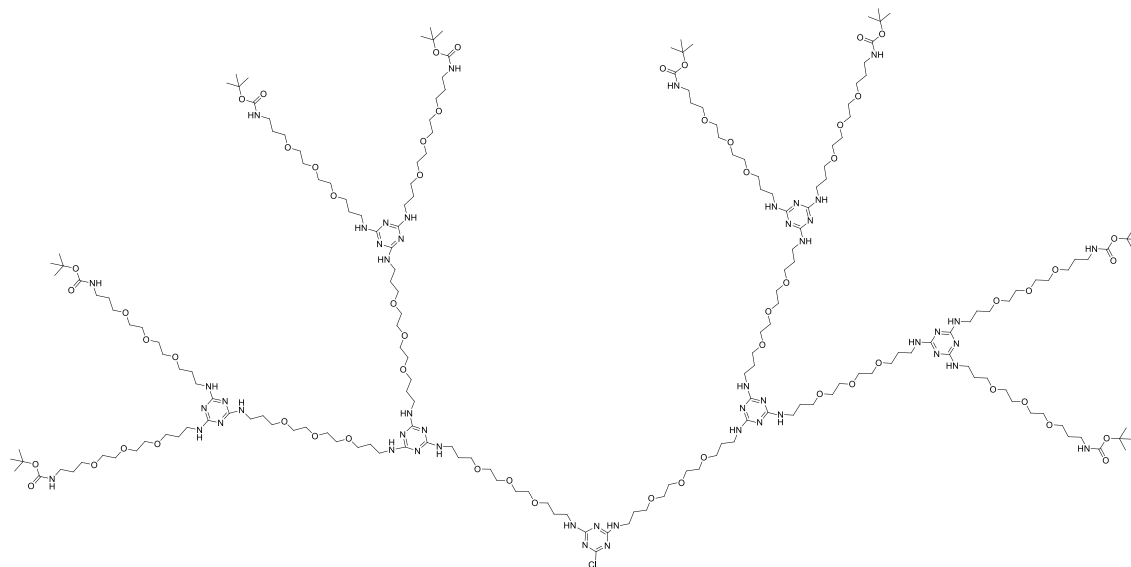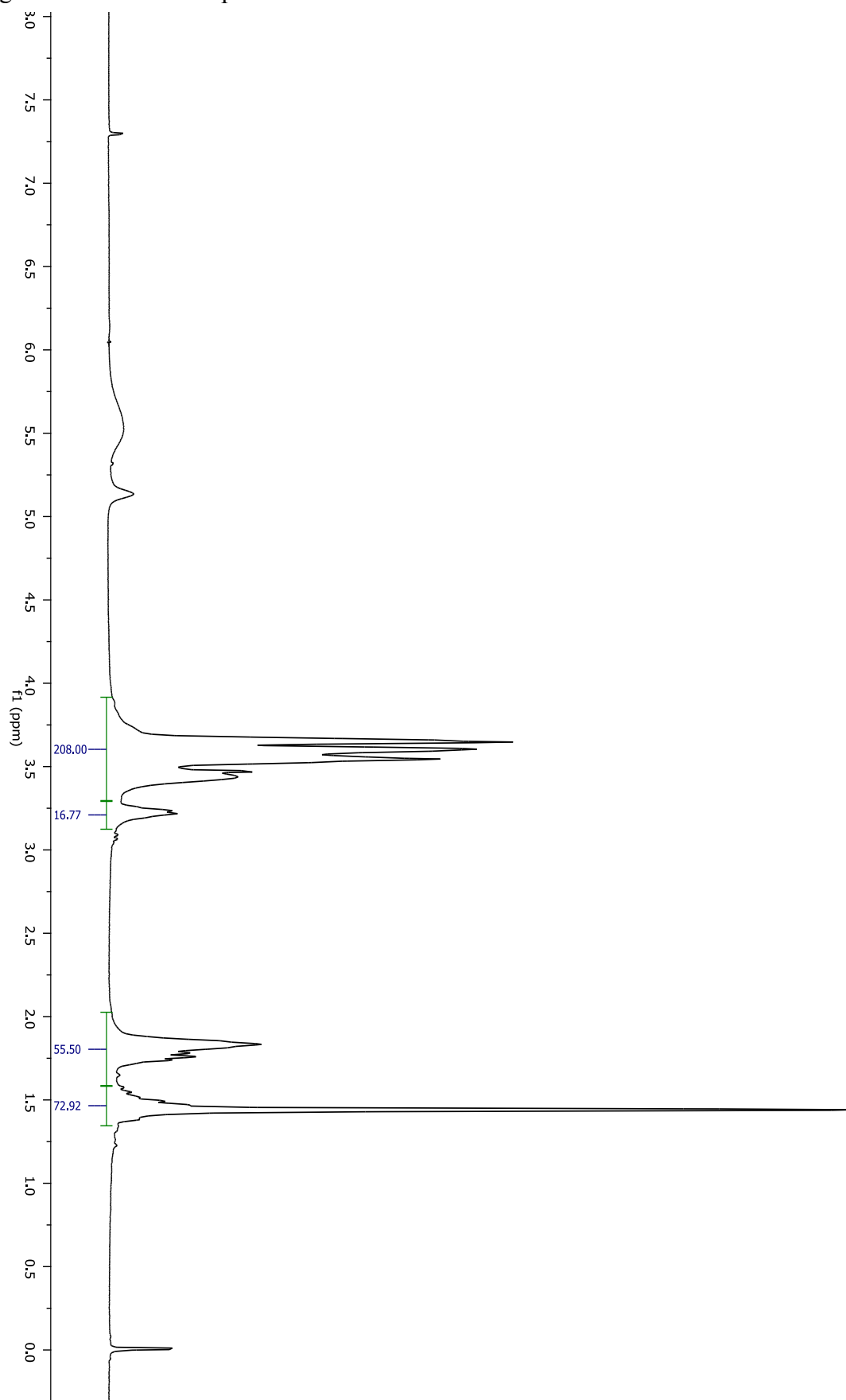
Figure S13. ^{1}H NMR Spectrum of **5**.

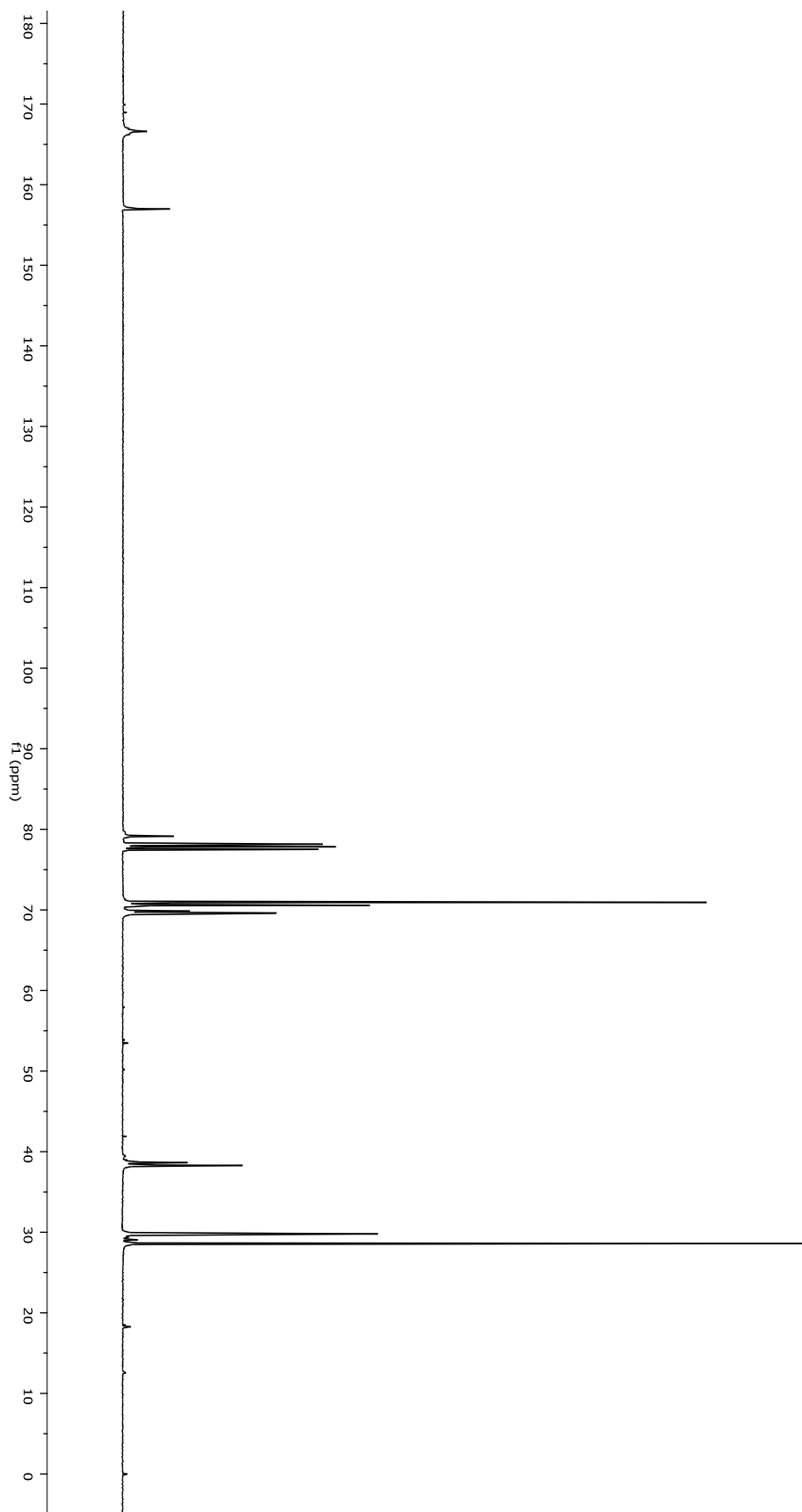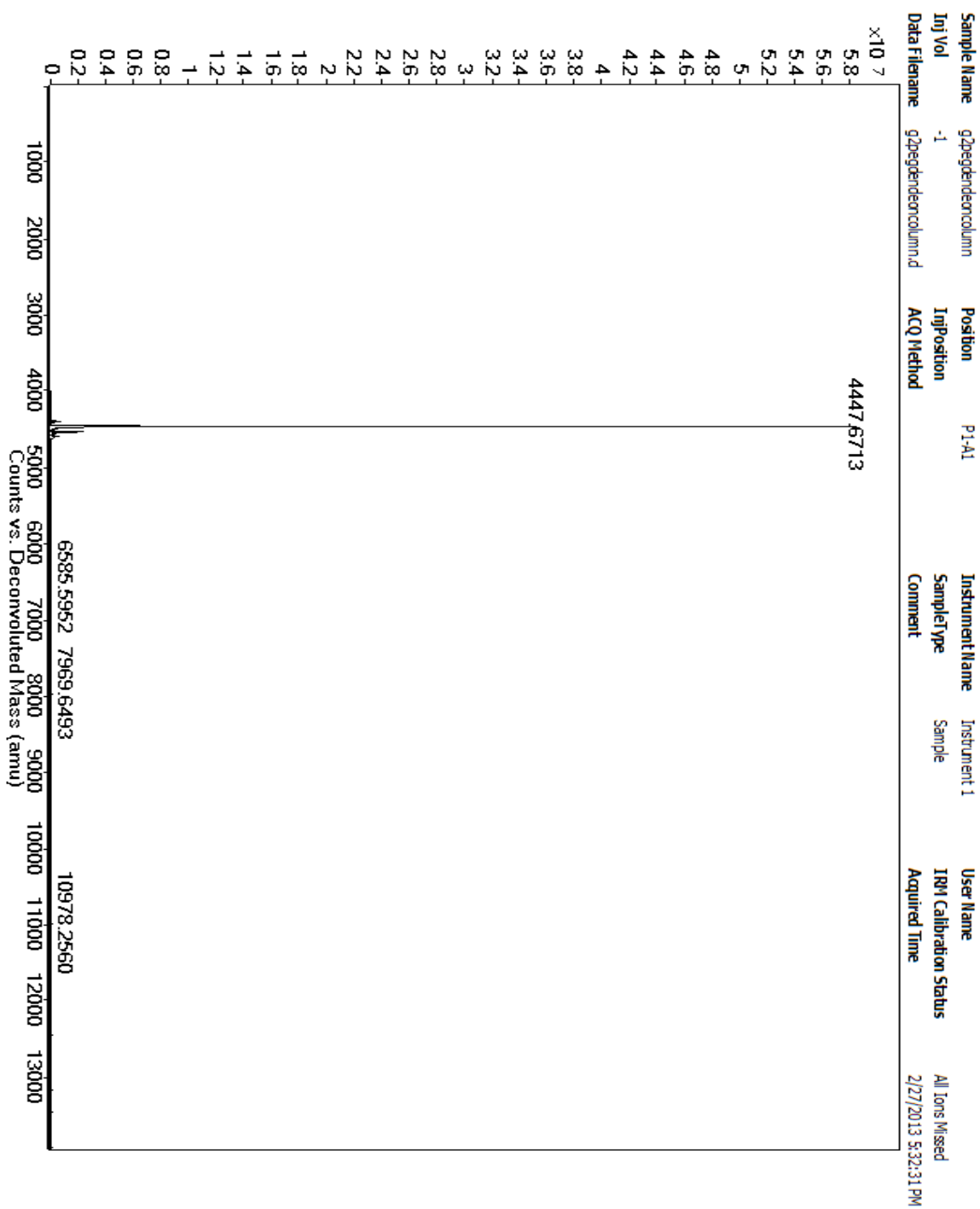Figure S14. ^{13}C NMR Spectrum of **5**

Figure S15. Mass Spectrum of **5**.

Compound 6 (G2.5) A solution of **5** (1.59 g, 0.36 mmol) with 4,7,10-trioxa-1,13-tridecanediamine (0.79g, 3.6 mmol) and Cs_2CO_3 (0.23g, 0.72 mmol) in 3.6 mL of 1,4 dioxane was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 30 minutes at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified twice by automated chromatography. The solvent system (in column volumes) used was the following: 1CV (100% DCM to 95:5=DCM:MeOH), 14CV (95:5=DCM:MeOH), 10CV (90:10= DCM: MeOH), 10CV (85:15= DCM: MeOH), 5CV (80:20= DCM: MeOH), 10CV (5:1:1% = DCM: MeOH: NH_4OH) to give **6** (1.35g, 82%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65-3.46 (m, 222H, **CH₂**O**CH₂**CH₂O**CH₂**CH₂O**CH₂**, C_3N_3-NHC**H₂**CH₂CH₂O), 3.21 (br m, 16H, BocNHC**H₂**), 2.0 (m, 2H, NH_2C**H₂**CH₂CH₂O) 1.84-1.73 (m, 60H, OCH₂C**H₂**CH₂), 1.43 (s, 72H, C(C**H₃**)₃); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.11 (**C**₃N₃), 157.0 (**C**O), 79.32 (**C**(CH₃)₃), 70.96 (O**C**H₂**C**H₂O), 70.66 (two lines, O**C**H₂**C**H₂O), 69.94 (CH₂**C**H₂CH₂O), 69.51 (CH₂**C**H₂CH₂O), 38.73 (NH₂**C**H₂CH₂CH₂O), 38.73 (**C**H₂CH₂CH₂O), 38.56 (**C**H₂CH₂CH₂O), not found (NH₂**C**H₂CH₂CH₂O), not found (NH**C**H₂CH₂CH₂O), 28.63 (C(**C**H₃)₃); MS (ESI-TOF) calcd for $C_{211}H_{403}N_{51}O_{61}$ 4628.0001, found 4632.2038(M + H)$^+$.
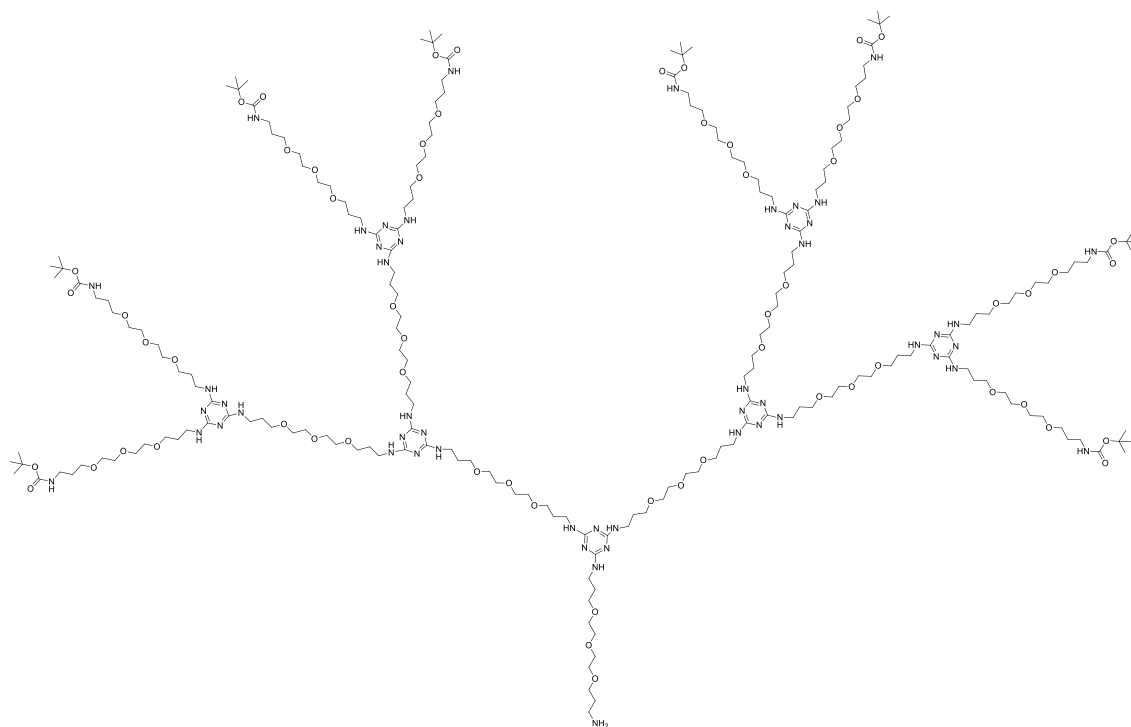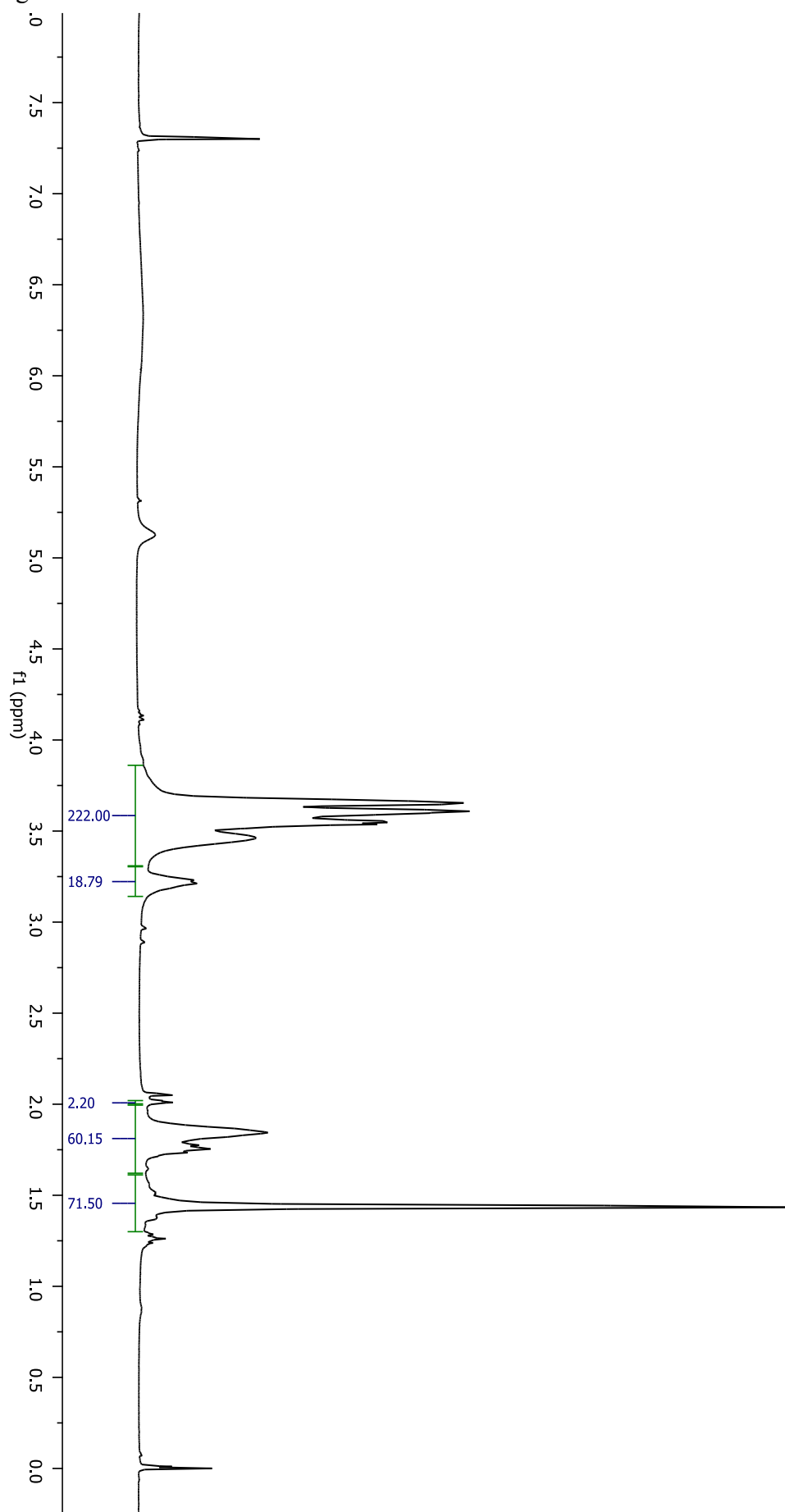
Figure S16. ¹H NMR of **6.**

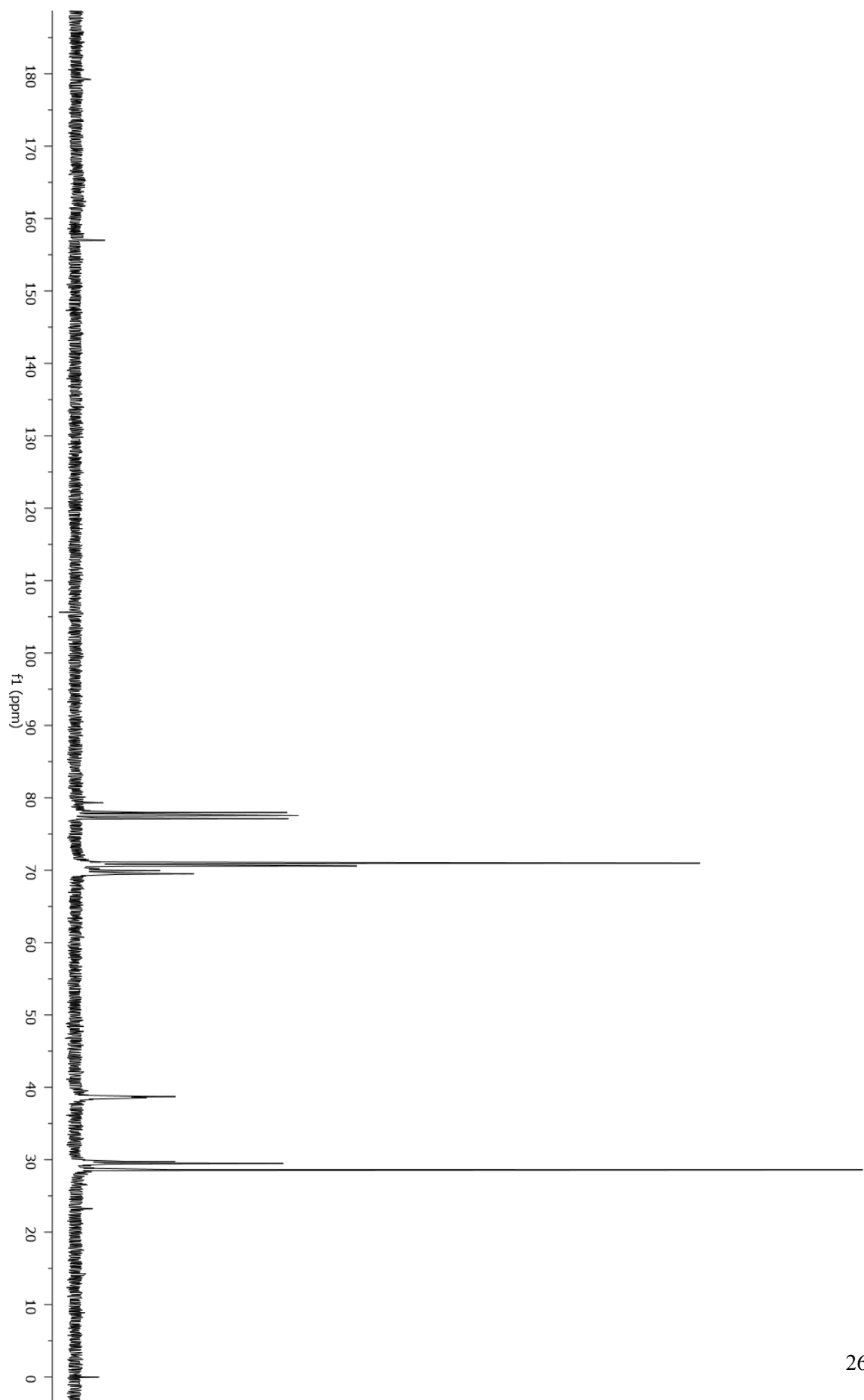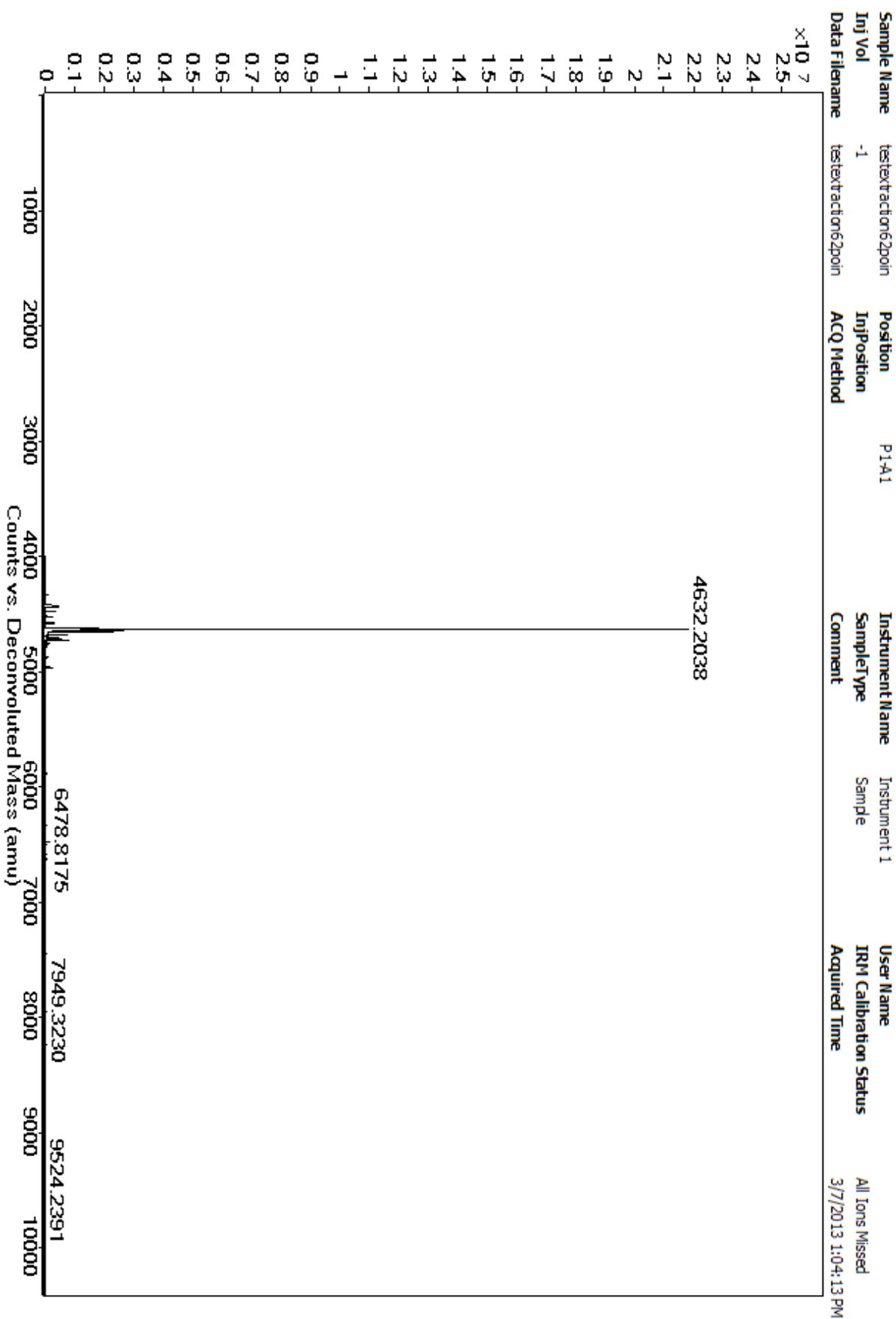Figure S17. ^{13}C NMR of **6.**

Figure S18. Mass Spectrum of **6.**

Compound 7 (G3-Cl) Compound **6** (1.05 g, 0.228 mmol) was added to a solution of cyanuric chloride (0.019 g, 0.104 mmol) in THF (2.3 mL), afterwards DIPEA was added dropwise (0.084 mL, 0.487 mmol). The solution was stirred for 2 minutes in order to allow reagents to mix. Then, the solution was irradiated in the microwave while stirring (CEM SP Discovery) for 10 minutes at 60ºC using dynamic mode. The crude product was purified twice by automated chromatography. The solvent system (in column volumes) used was the following: 1 CV (100% DCM to 95:5= DCM: MeOH), 14CV (95:5= DCM: MeOH), 10CV (90:10= DCM: MeOH), 10CV (85:15= DCM: MeOH), 15CV (80:20= DCM: MeOH) to give **7** (1.49g, 70%) as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.64-3.42 (m, 448H, **CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.21 (br m, 32H, BocNHC**H$_2$**), 1.83-1.74 (m, 120H, OCH$_2$C**H$_2$**CH$_2$), 1.44 (s, 144H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.04 (**C**$_3$N$_3$), 154.36 (**C**O), 80.05(**C**(CH$_3$)$_3$), 70.98 (O**CH$_2$CH$_2$**O), 70.61 (two lines, O**CH$_2$CH$_2$**O), 69.94 (**CH$_2$CH$_2$CH$_2$**O), 69.64 (**CH$_2$CH$_2$CH$_2$**O), 38.73 (**CH$_2$CH$_2$CH$_2$**O), 38.30(**CH$_2$CH$_2$CH$_2$**O), 29.84 (NH**CH$_2$CH$_2$CH$_2$**O), 28.62 (C(**CH$_3$**)$_3$); MS (ESI-TOF) calcd for C$_{425}$H$_{804}$ClN$_{105}$O$_{122}$ 9366.9625, found 9374.7207(M + H)$^+$.
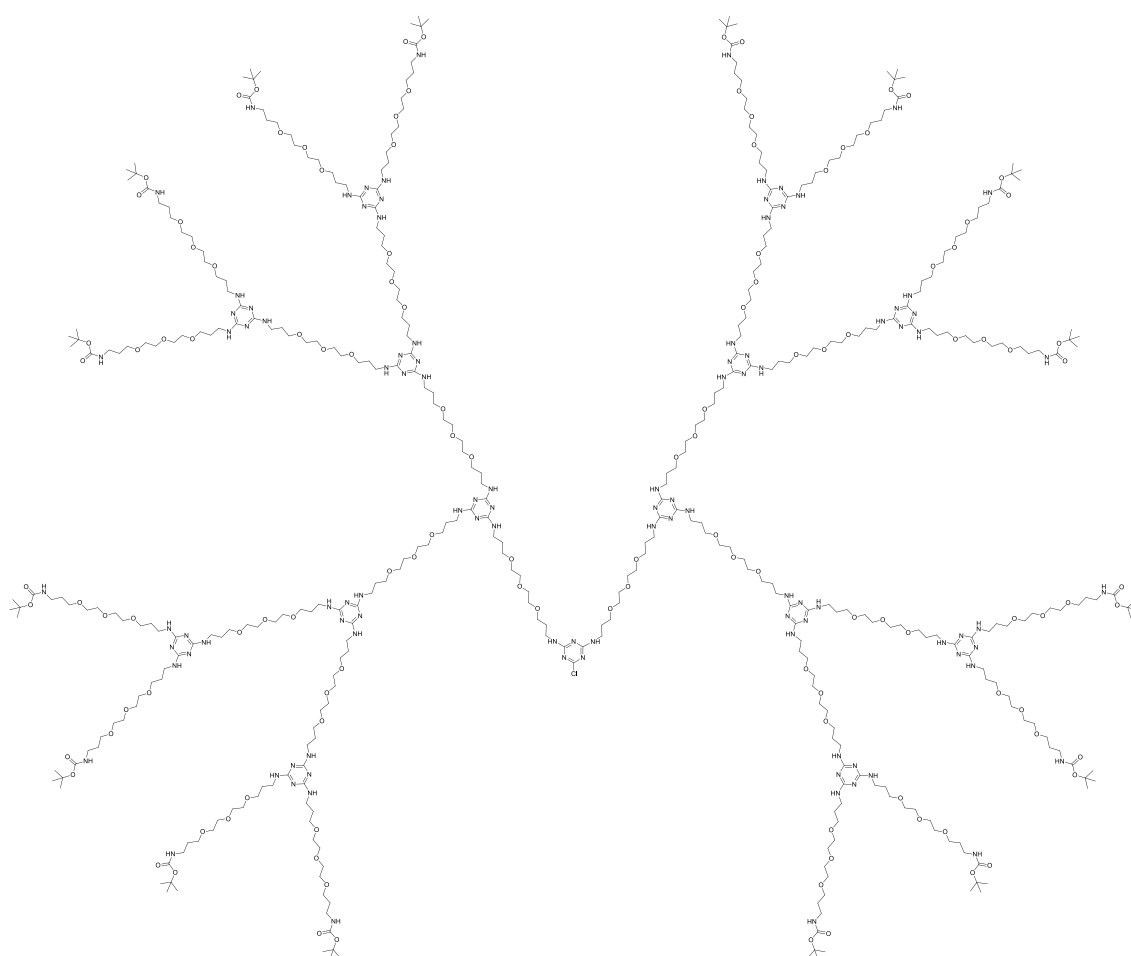
Figure S19. ^{1}H NMR of **7.**
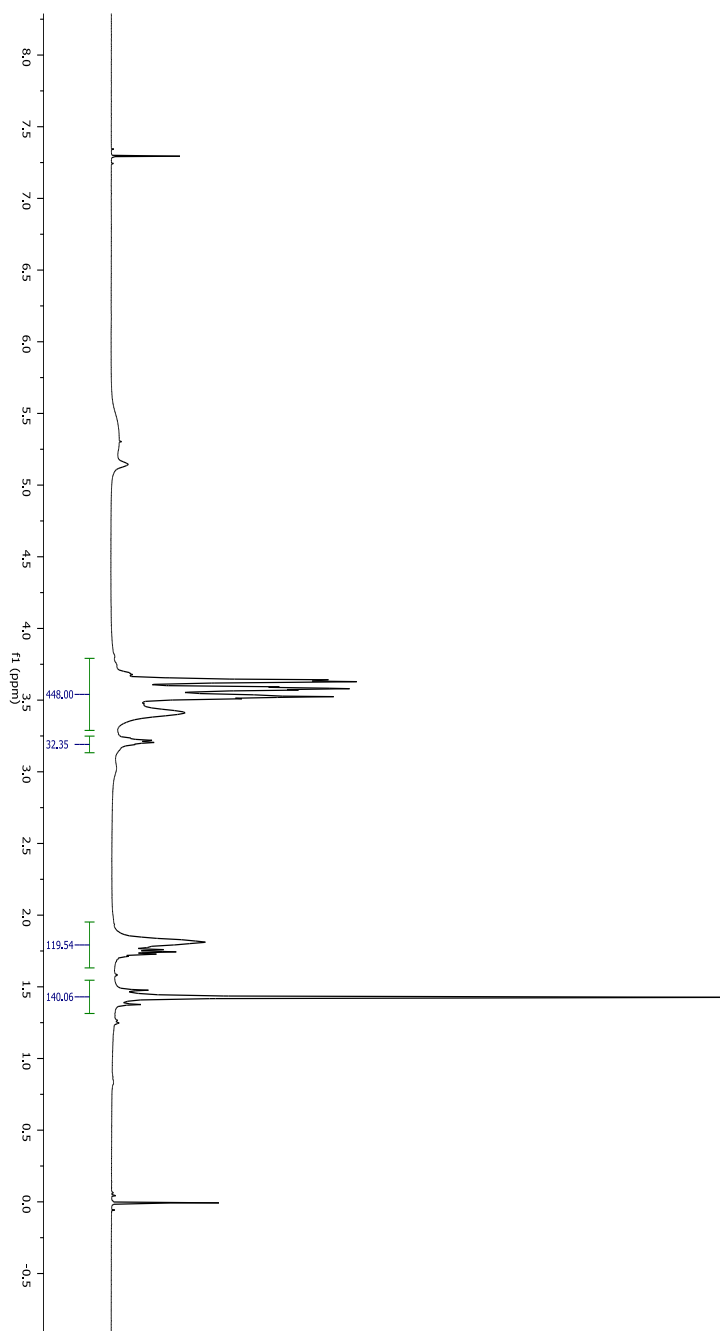
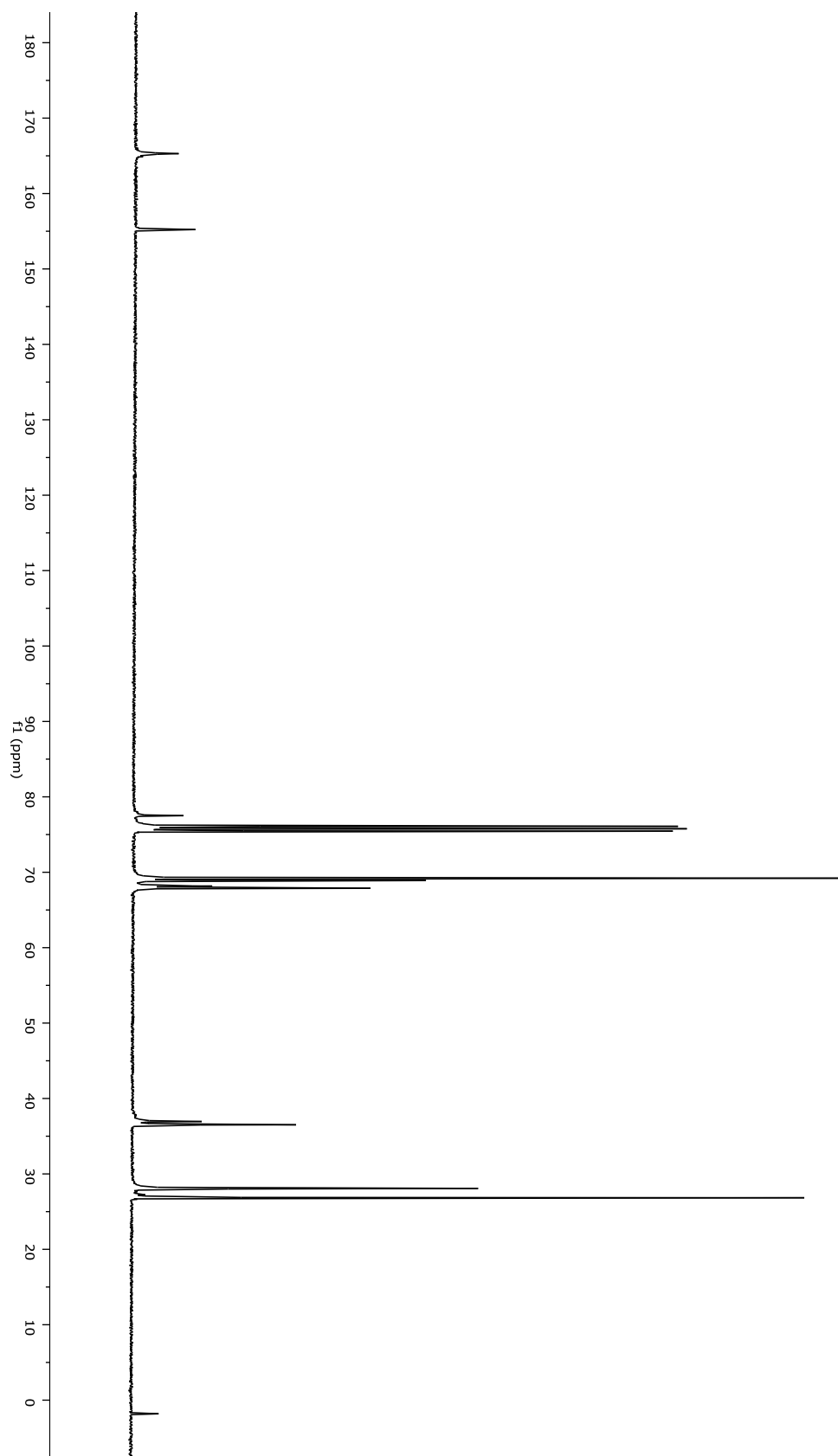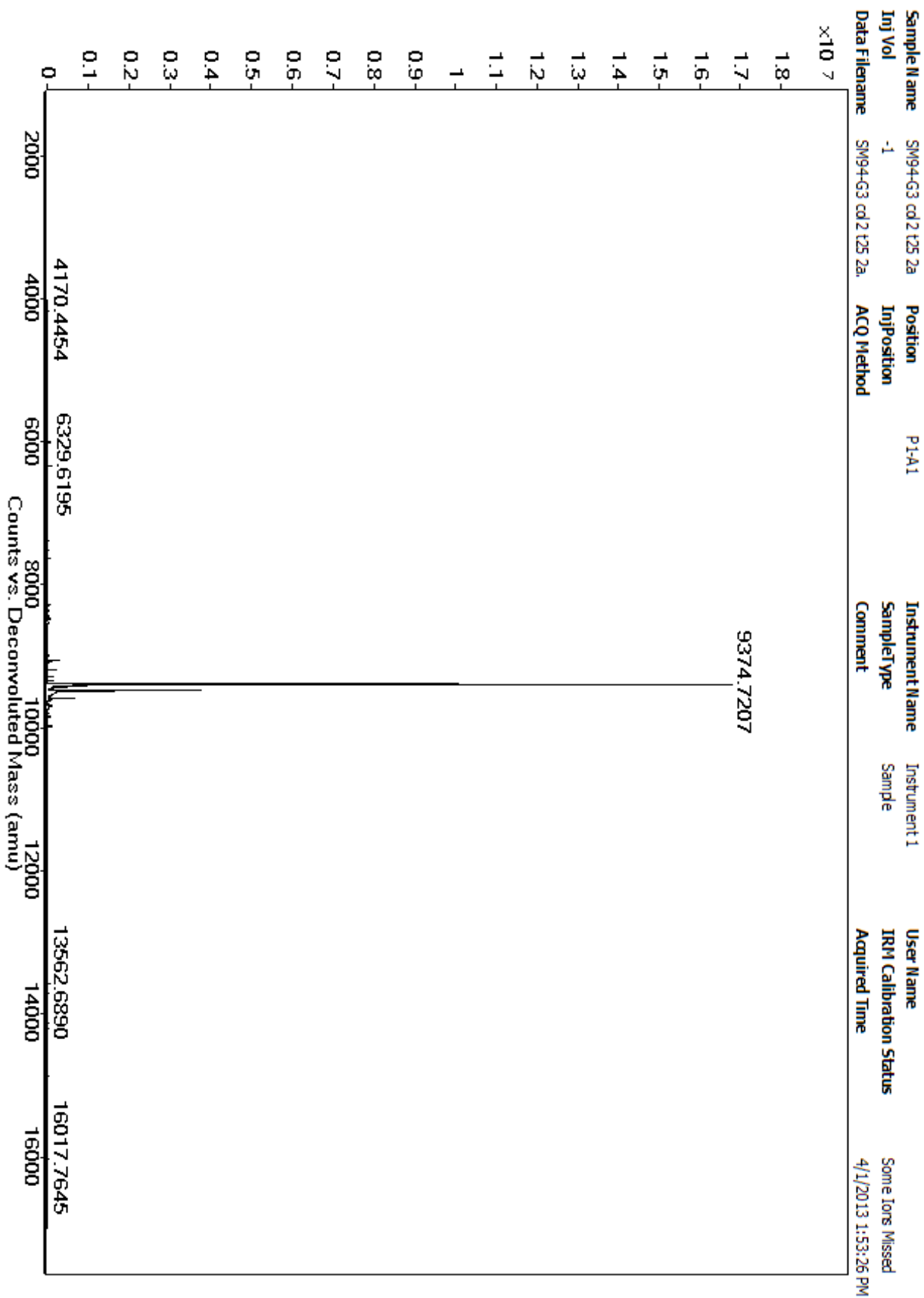Figure S20. ^{13}C NMR Spectrum of **7.**

Figure S21. Mass spectrum of **7.**

Compound 8 (G1-alkyne). A solution of propargylamine (0.136 g, 2.48 mmol), **1** (0.492 g, 0.248 mmol), and Cs_2CO_3 (0.242 g, 0.741 mmol) in dioxane (2.5 mL) was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for three periods of 30 minutes at 95ºC using dynamic mode. In each extra period were added 10 equivalents more of propargylamine (0.408g, 7.44 mmol) to give a total of 30 equivalents in the final solution. Afterwards, the reaction mixtures was evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by silica gel chromatography (DCM:MeOH = 10:1) to give **8** (0.46 g, 93%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (br, 2H, HC≡CC**H$_2$**), 3.65-3.43 (m, 88H, **CH$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**C**H$_2$**C**H$_2$**O), 3.21 (br m, 8H, BocNHC**H$_2$**), 2.23 (br, 1H, **H**C≡CC**H$_2$**), 1.85-1.73 (m, 24H, OCH$_2$C**H$_2$**CH$_2$), 1.43 (s, 36H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.59 (br, **C**$_3$N$_3$), 156.98 (**C**O), 81.85 (HC≡**C**CH$_2$), 79.32 (**C**(CH$_3$)$_3$), 70.7 (H**C**≡CCH$_2$), 70.96 (O**C**H$_2$**C**H$_2$O), 69.95 (O**C**H$_2$**C**H$_2$O), 69.93 (O**C**H$_2$**C**H$_2$O) 69.67 (CH$_2$**C**H$_2$CH$_2$O), 69.56 (CH$_2$C**H$_2$**CH$_2$O), 38.71 (**C**H$_2$CH$_2$CH$_2$O), 38.35 (**C**H$_2$CH$_2$CH$_2$O), not found (HC≡**C**CH$_2$), 28.61 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{92}H_{172}N_{22}O_{26}$ 2001.2813, found 2002.2499 $(M + H)^+$.
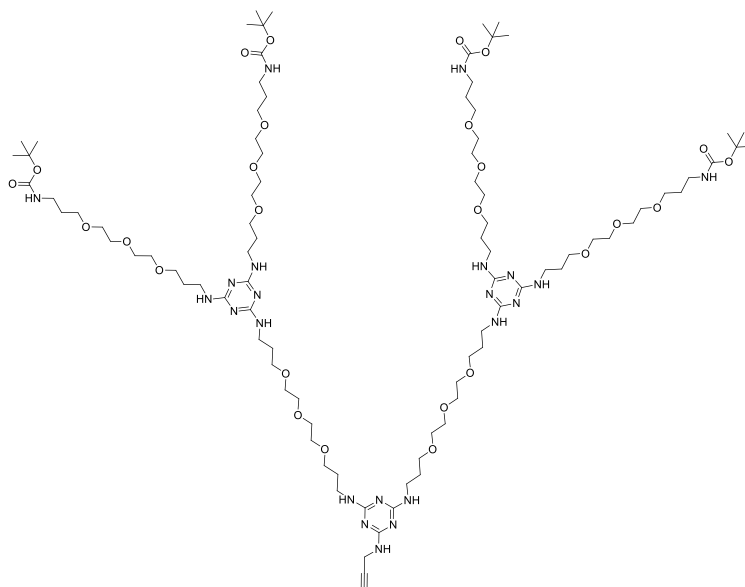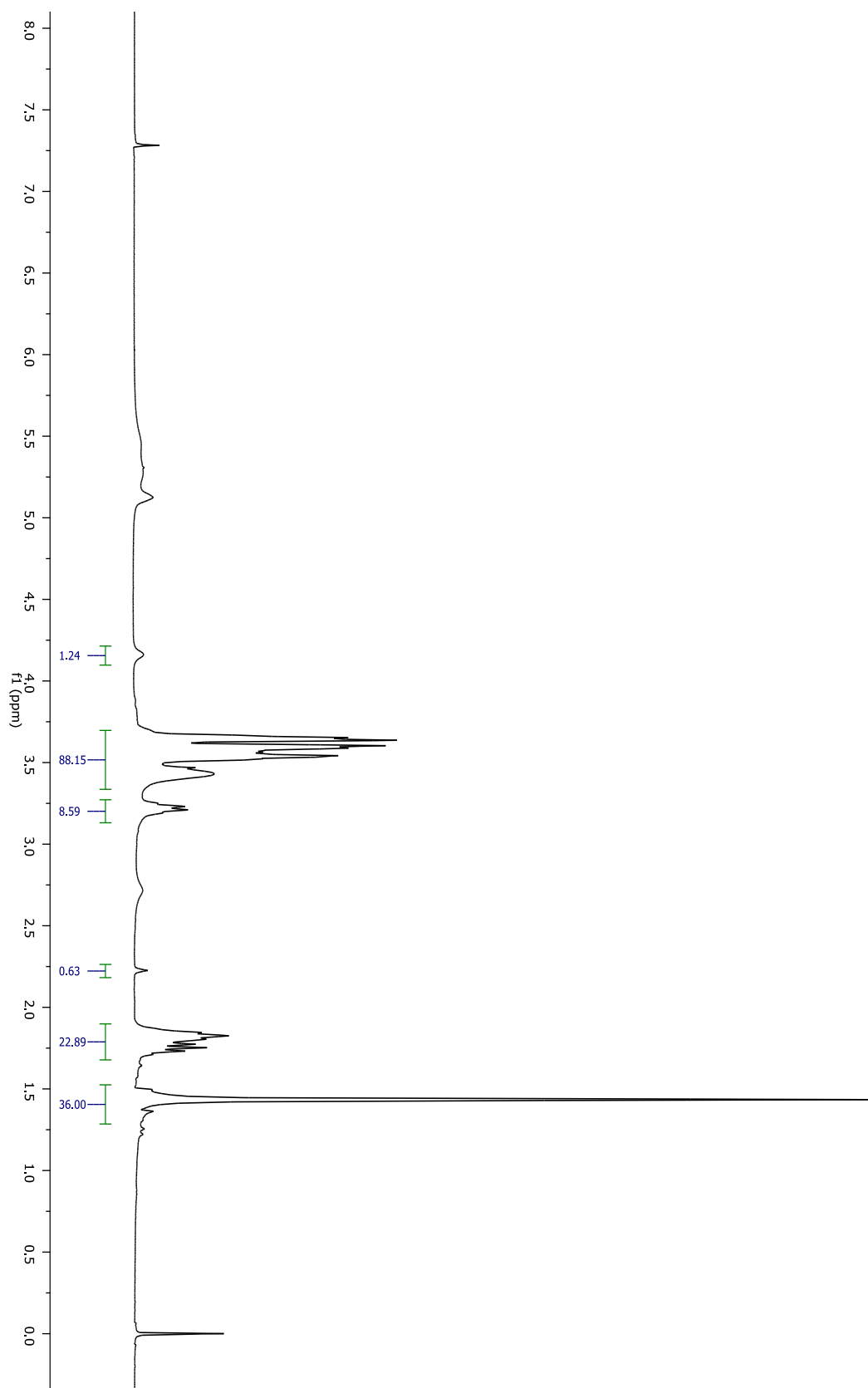
Figure S22. ^{1}H NMR Spectrum of **8.**

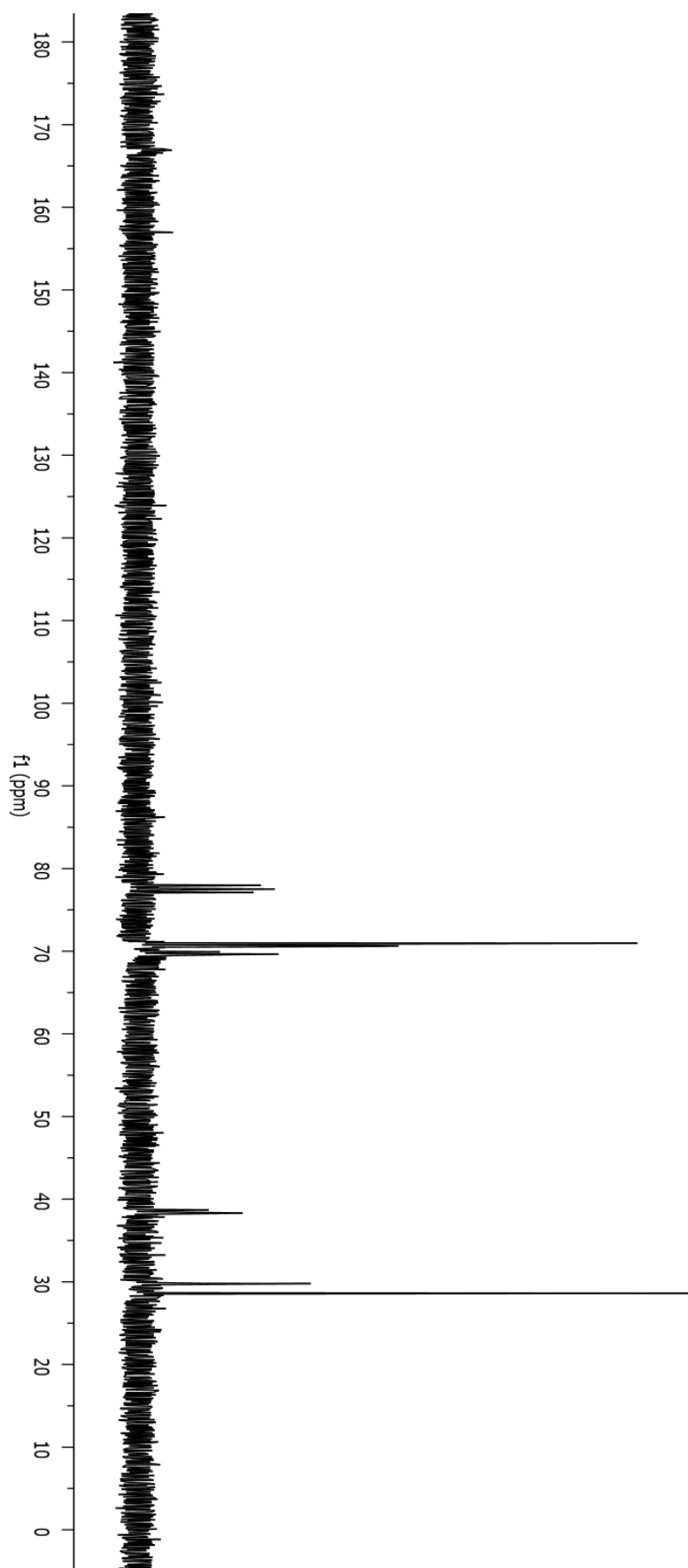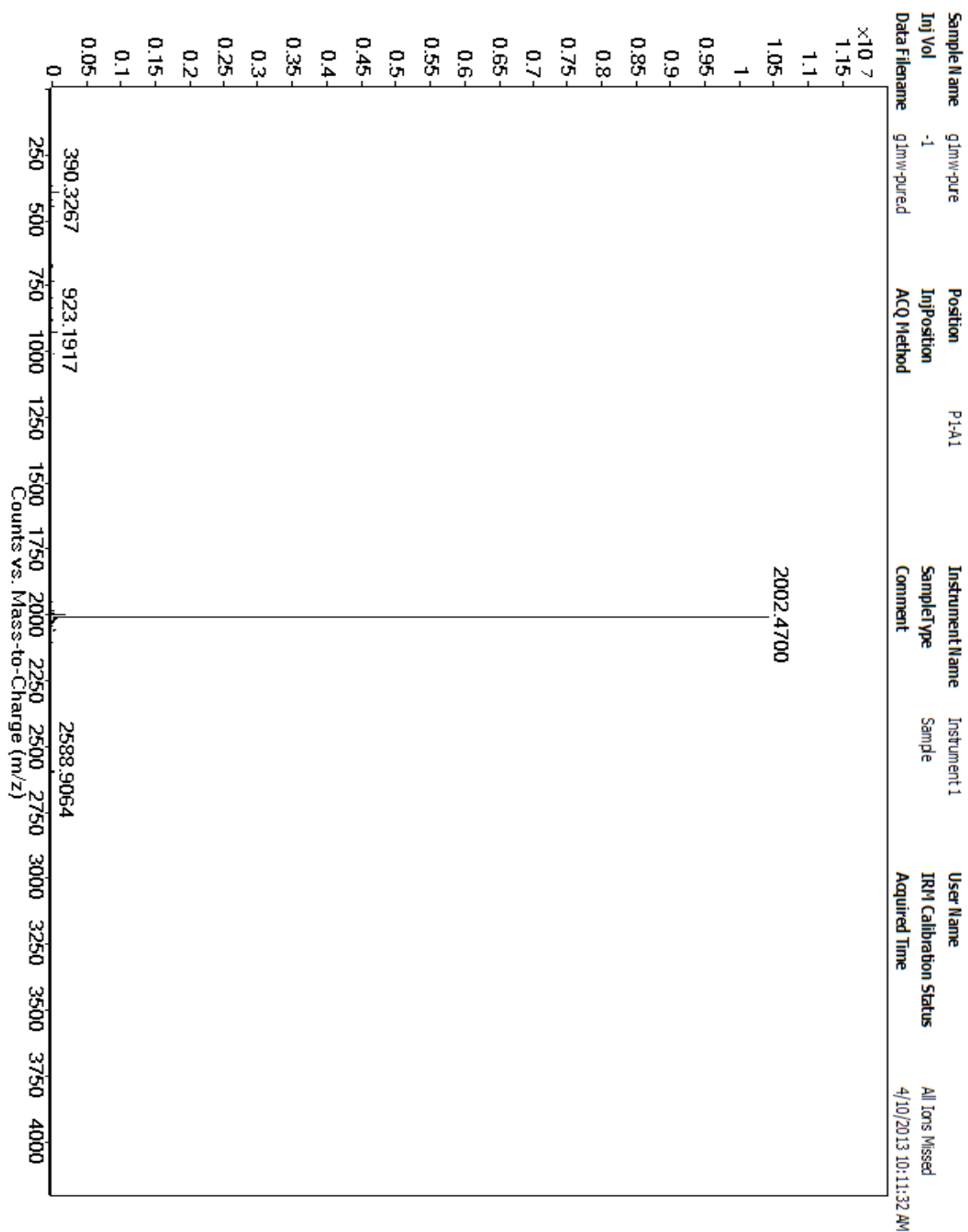Figure S23. ^{13}C NMR Spectrum of **8.**

Figure S24. Mass Spectrum of **8.**

Compound 9. A solution of **8** (0.800 g, 0.4 mmol) in concentrated HCl (1.5 mL) and methanol (3 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for two periods of 3 minutes at 60ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **9** (0.640 g, quantitative) as a clear oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.21 (br, 2H, HC≡CC**H$_2$**), 3.69-3.47 (m, 88H, **CH$_2$**OC**H$_2$CH$_2$**OC**H$_2$CH$_2$**OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$CH$_2$**CH$_2$O), 2.85 (br, 8H, OCH$_2$CH$_2$C**H$_2$**NH$_2$), 2.30 (br, 1H, **H**C≡CCH$_2$), 1.87-1.76 (m, 24H, OCH$_2$**CH$_2$**CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.89 (**C$_3$**N$_3$), 70.84 (HC≡**C**CH$_2$), 70.80 (HC≡C**C**H$_2$, O**C**H$_2$CH$_2$O), 70.46 (O**C**H$_2$**C**H$_2$O), 70.39 (O**C**H$_2$**C**H$_2$O) 69.63 (CH$_2$**C**H$_2$CH$_2$O), 69.49 (two lines, CH$_2$**C**H$_2$**C**H$_2$O), 39.63 (**C**H$_2$CH$_2$CH$_2$O), 38.08 (CH$_2$**C**H$_2$CH$_2$O), 33.33 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 30.13 (HC≡CC**H$_2$**), 29.67 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for C$_{72}$H$_{140}$N$_{22}$O$_{18}$ 1601.0716, found 1602.0498 (M + H)$^+$.
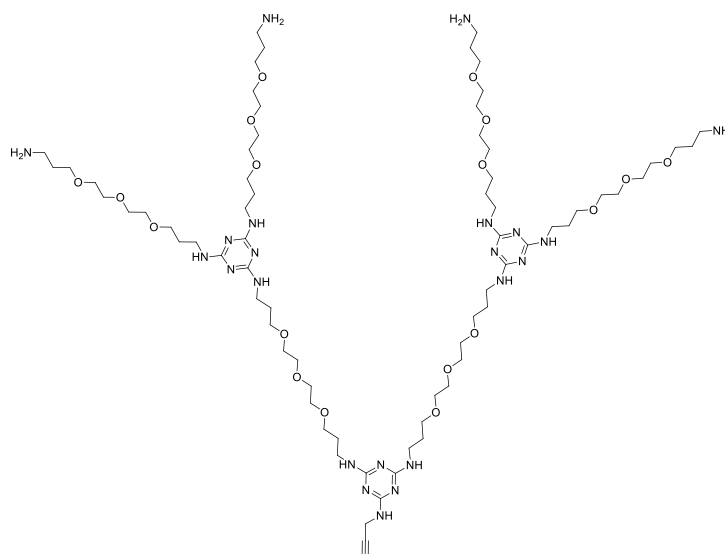
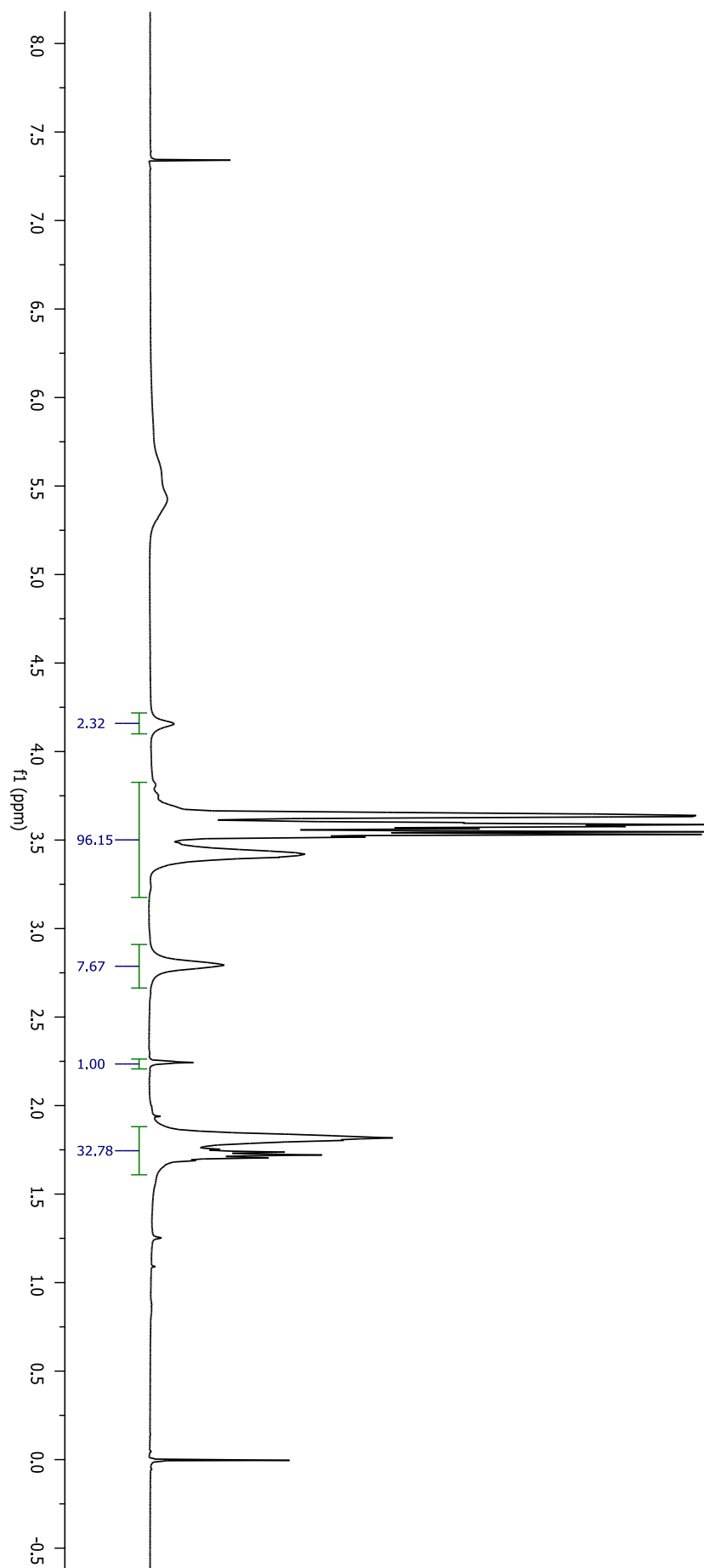Figure S25. ¹H NMR Spectrum of **9.**

Figure S26. ^{13}C NMR Spectrum of **9.**
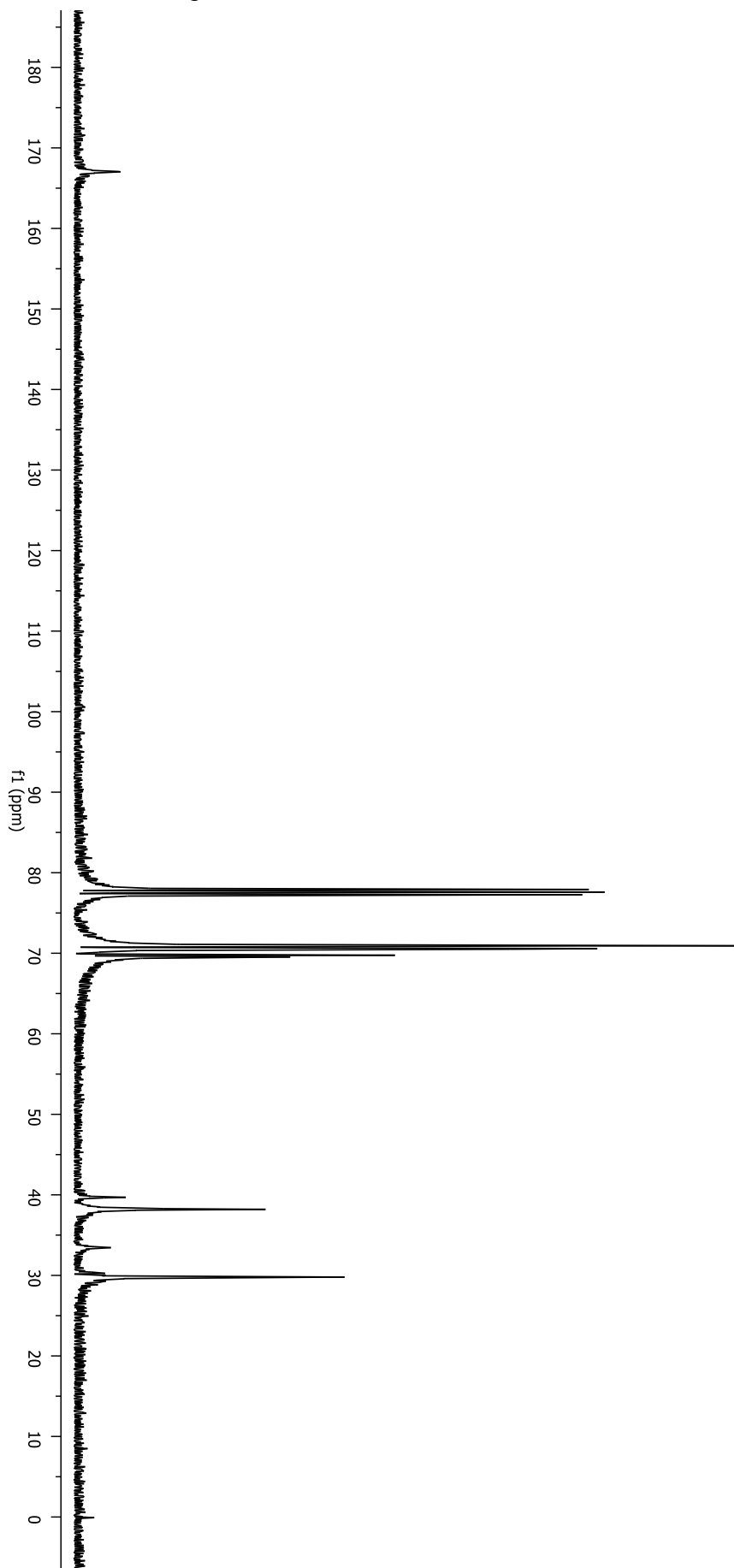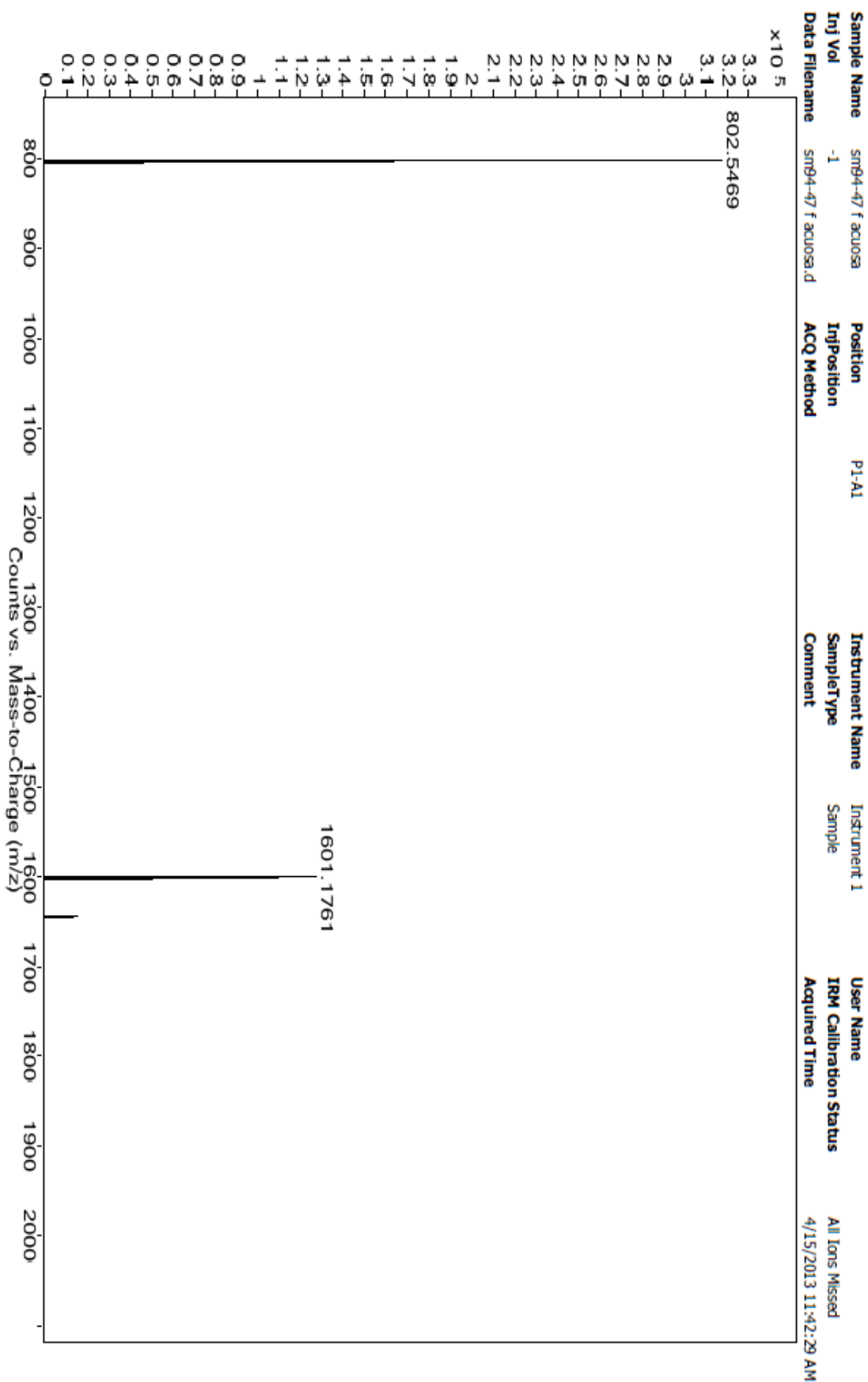

f1 (ppm)

Figure S27. Mass Spectrum of **9.**

Compound 10 (G2 alkyne). A solution of propargylamine (0.0125 g, 0.2245 mmol), **5** (0.100 g, 0.022 mmol), and Cs_2CO_3 (0.022g, 0.066 mmol) in dioxane (0.3 mL) was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring (CEM SP Discovery) for three periods of 30 minutes at 95ºC using dynamic mode. In each extra period were added 10 equivalents more of propargylamine (0.0375g, 0.6735mmol) to give a total of 30 equivalents in the final solution and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by silica gel chromatography (DCM:MeOH = 10:1 to DCM:MeOH = 7:1) to give **10** (0.093 g, 93%) as a clear oil. ^1H NMR (300 MHz, CDCl$_3$) δ 4.16 (br, 2H, HC≡CC**H$_2$**), 3.64-3.43 (m, 102H, C**H$_2$**OC**H$_2$**CH$_2$OC**H$_2$**CH$_2$OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.21 (br m, 16H, BocNHC**H$_2$**), 2.25 (br, 1H, **H**C≡CCH$_2$), 1.82-1.73 (m, 56H, OCH$_2$C**H$_2$**CH$_2$), 1.43 (s, 72H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.82 (br, **C**$_3$N$_3$), 157.03 (**C**O), not found (HC≡C**C**H$_2$), 79.34 (**C**(CH$_3$)$_3$), 70.7 (HC≡**C**CH$_2$), 70.96 (O**C**H$_2$CH$_2$O), 69.95 (OCH$_2$**C**H$_2$O), 69.93 (O**C**H$_2$CH$_2$O) 69.67 (**C**H$_2$CH$_2$CH$_2$O), 69.56 (CH$_2$CH$_2$**C**H$_2$O), 38.78 (**C**H$_2$CH$_2$CH$_2$O), 38.40 (CH$_2$**C**H$_2$CH$_2$O), not found (H**C**≡CCH$_2$), 29.85 (NHCH$_2$**C**H$_2$CH$_2$O), 28.65 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{204}H_{348}N_{50}O_{58}$ 4462.8636 found 4464.9714 $(M + H)^+$.
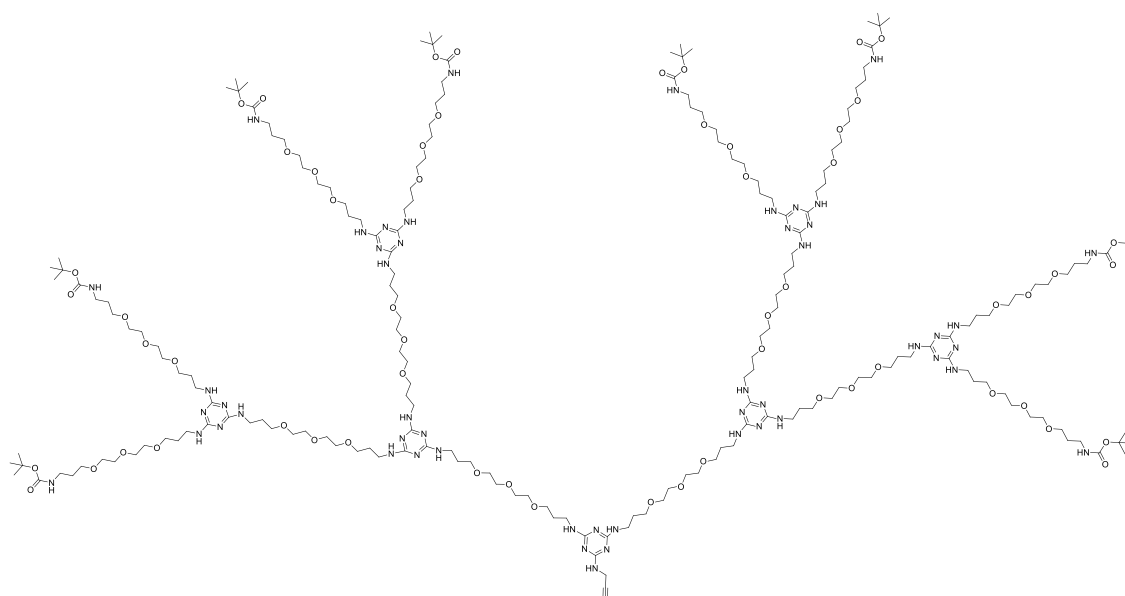
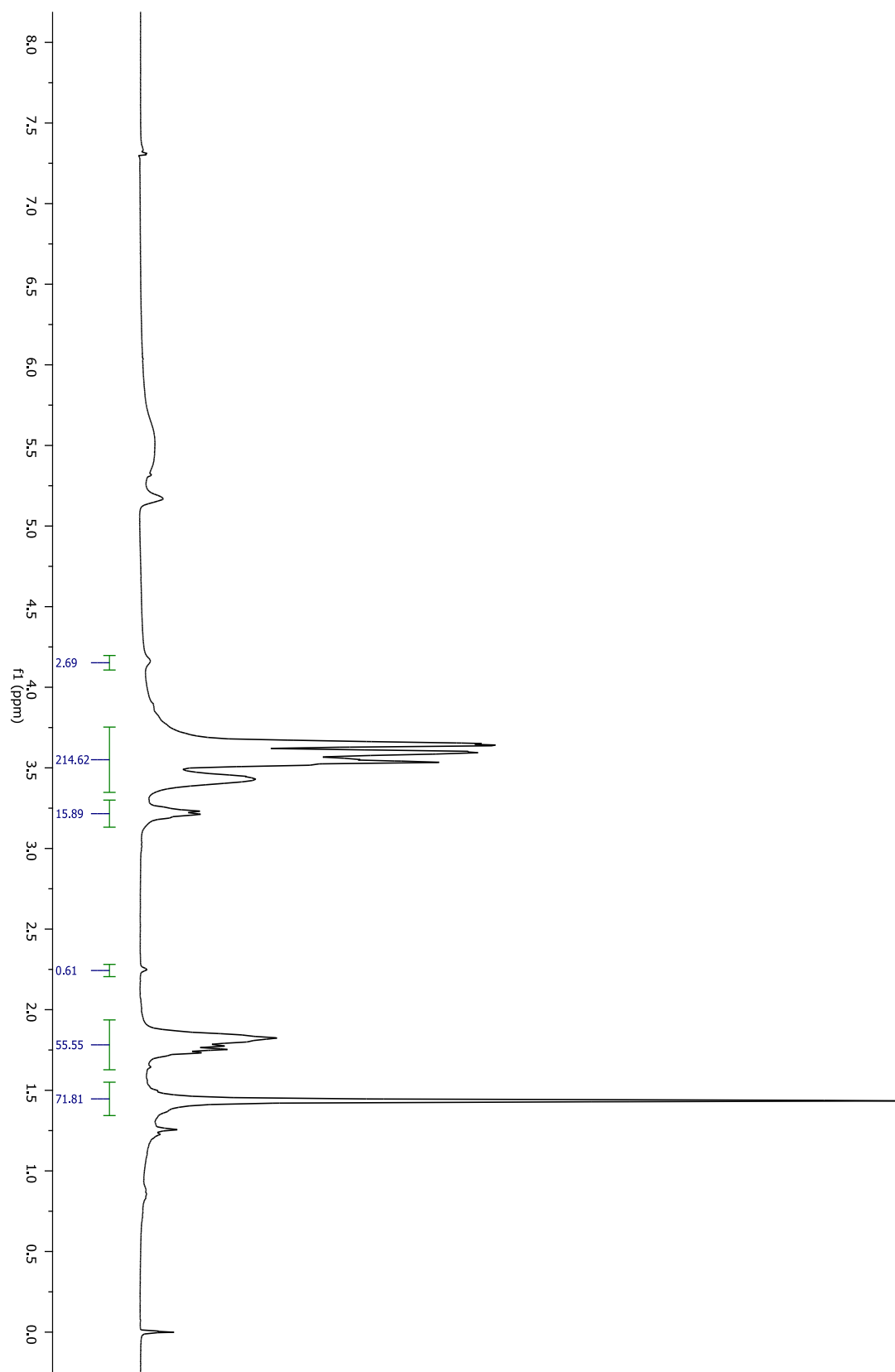Figure S28. ^{1}H NMR Spectrum of **10.**

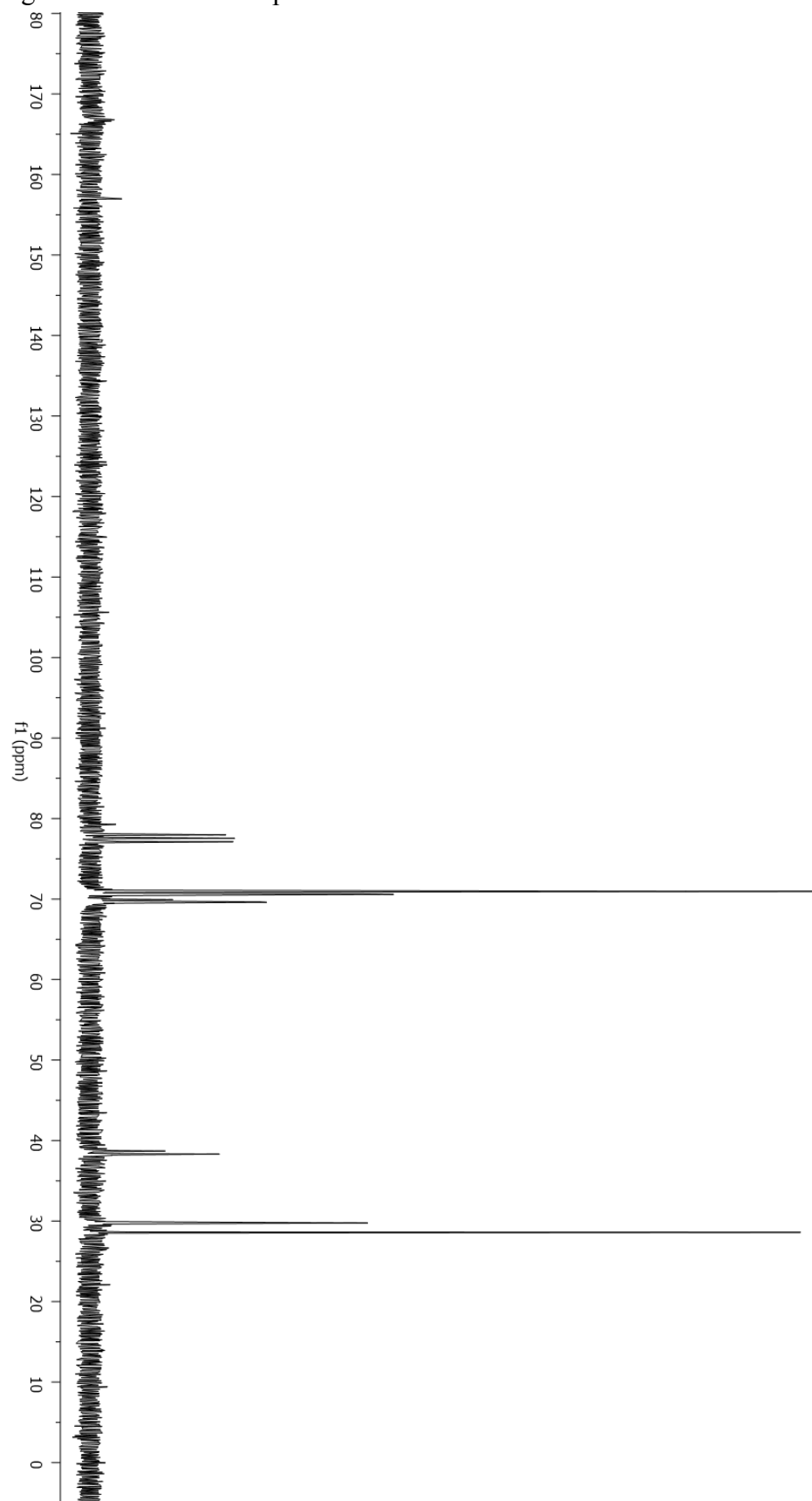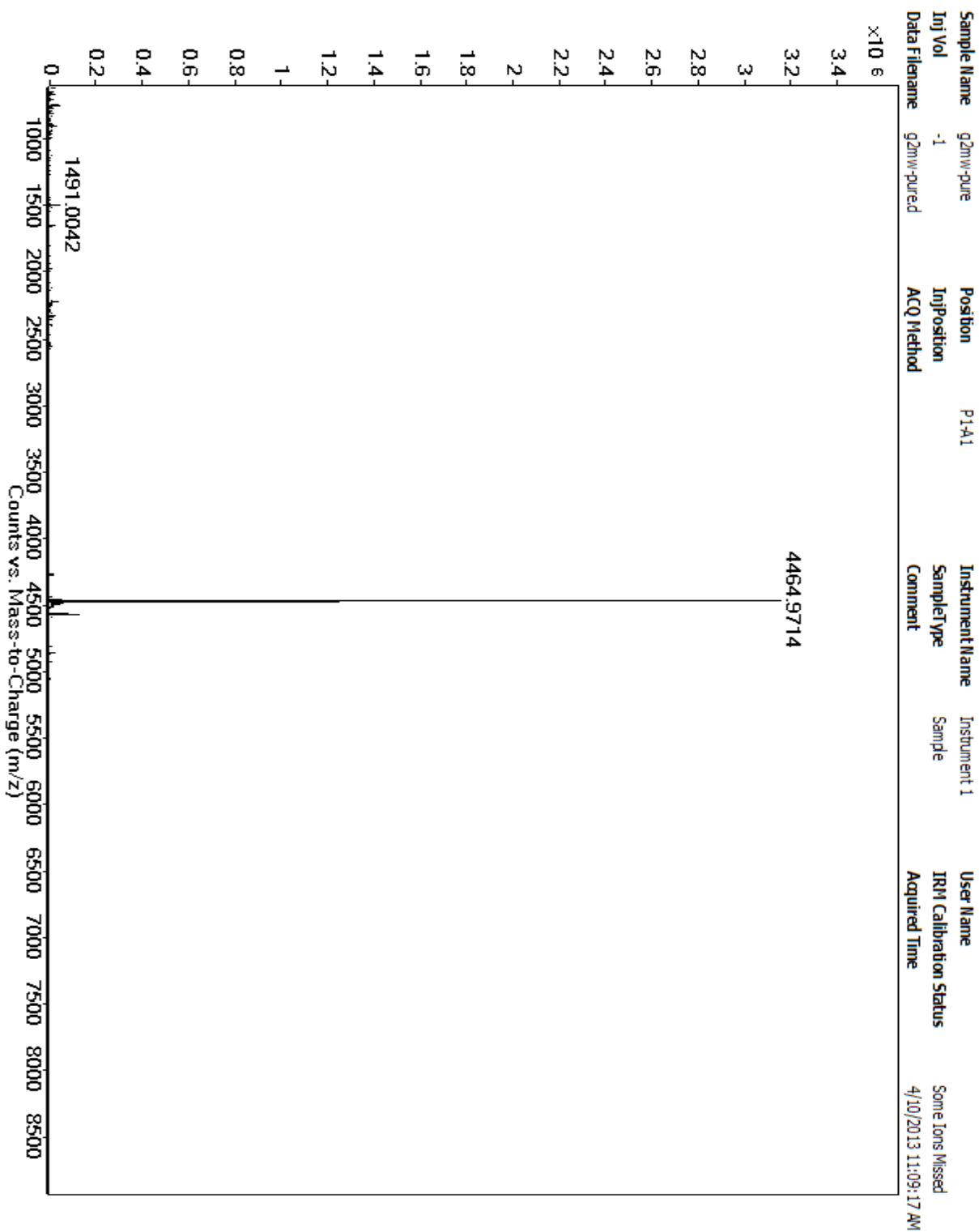Figure S29. ^{13}C NMR Spectrum of **10.**

Figure S30. Mass Spectrum of **10.**

Compound 11. A solution of **10** (0.093 g, 0.020 mmol) in concentrated HCl (0.5 mL) and methanol (1 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring (CEM SP Discovery) for two periods of 3 minutes at 60ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over MgSO$_4$, filtered, and evaporated under vacuum to give **11** (0.075 g, quantitative) as a clear oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.14 (br, 2H, HC≡C**CH$_2$**), 3.62-3.40 (m, 102H, **CH$_2$**OC**H$_2$CH$_2$**OC**H$_2$CH$_2$**OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 2.77 (br, 16H, OCH$_2$CH$_2$C**H$_2$**NH$_2$), 2.21 (br, 1H, **H**C≡CCH$_2$), 1.80-1.68 (m, 56H, OCH$_2$C**H$_2$**CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.94 (**C**$_3$N$_3$), 81.1 (HC≡**C**CH$_2$), not found (H**C**≡CCH$_2$, O**CH$_2$CH$_2$**O), 70.88 (O**CH$_2$CH$_2$**O), 70.49 (two lines, O**CH$_2$CH$_2$**O) 69.66 (**CH$_2$**CH$_2$CH$_2$O), 69.48 (two lines, CH$_2$**CH$_2$**CH$_2$O), 39.63 (**CH$_2$**CH$_2$CH$_2$O), 38.13 (**CH$_2$**CH$_2$CH$_2$O), 33.44 (OCH$_2$**CH$_2$**CH$_2$NH$_2$), not found (HC≡**C**CH$_2$), 29.7 (NHCH$_2$**CH$_2$**CH$_2$O); MS (ESI-TOF) calcd for C$_{164}$H$_{320}$N$_{50}$O$_{42}$ 3662.4441, found 3664.5145 (M + H)$^+$.
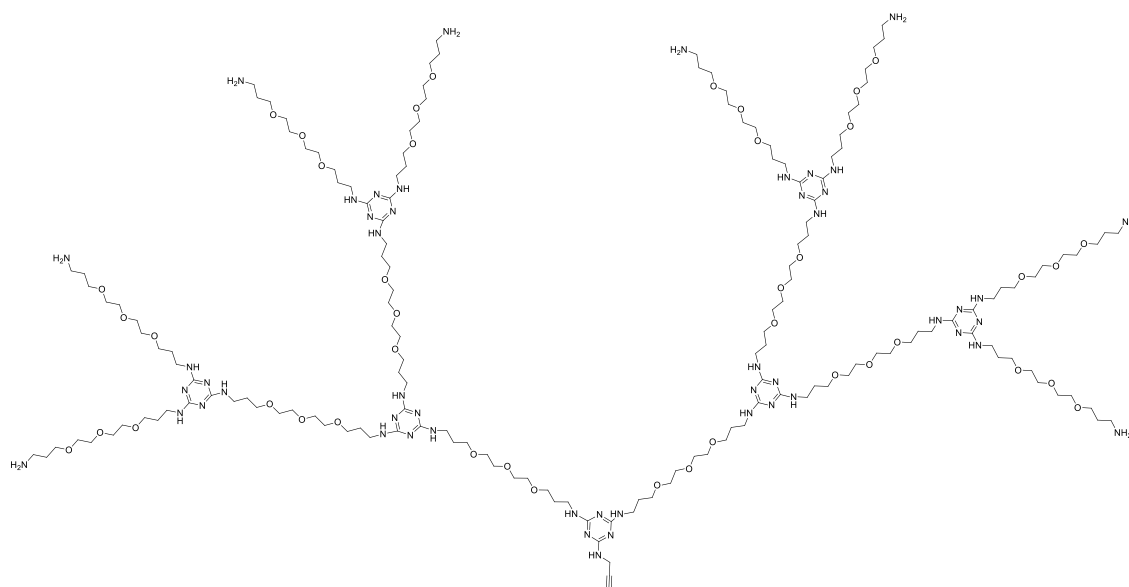
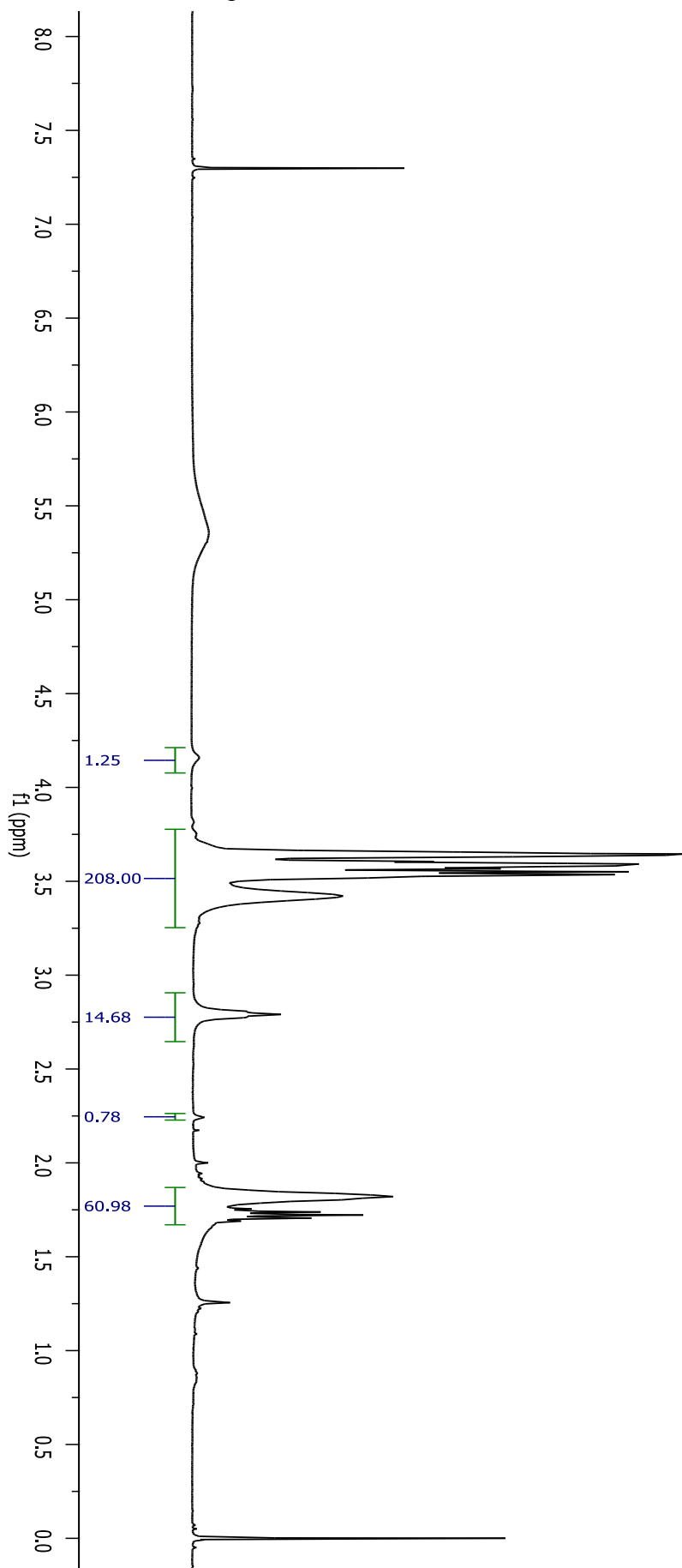Figure S31. ^{1}H NMR Spectrum of **11.**

Figure S32. ^{13}C NMR Spectrum of **11.**

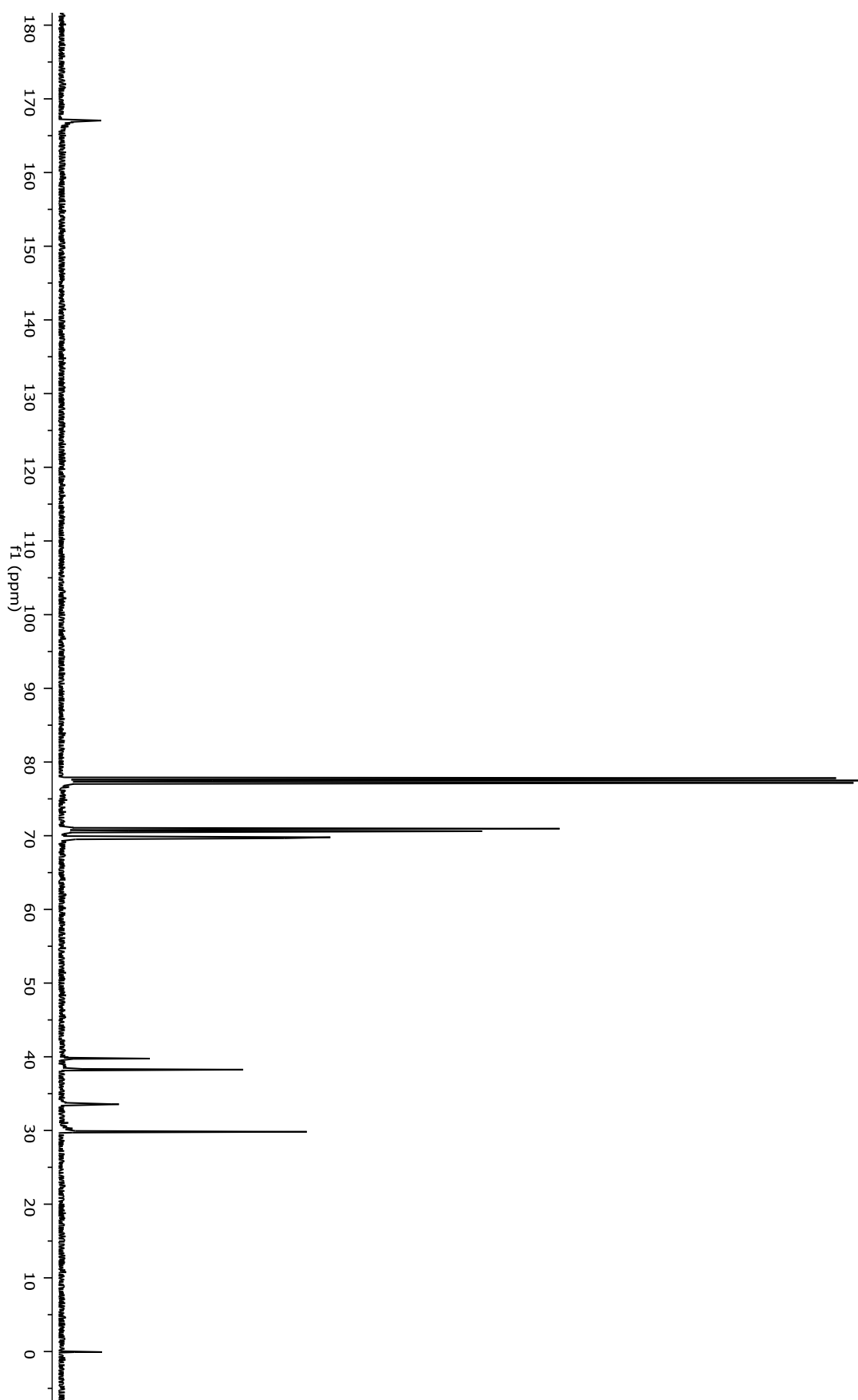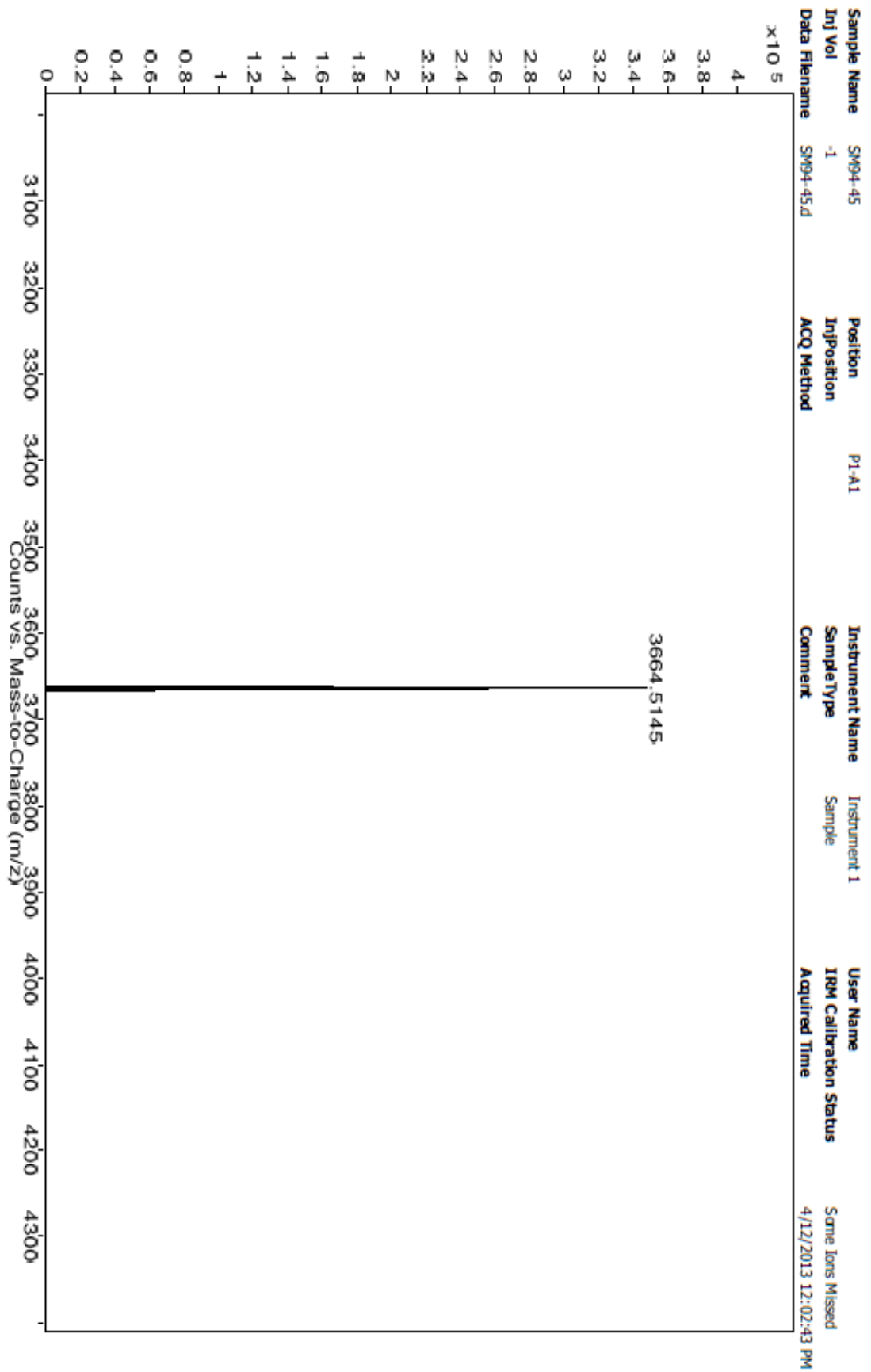Figure S33. Mass Spectrum of **11.**

Compound 12. A solution of propargylamine (0.0076 g, 0.0137 mmol), **7** (0.128 g, 0.0137 mmol), and Cs_2CO_3 (0.0145g, 0.041 mmol) in dioxane (0.2 mL) was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for three periods of 30 minutes at 95ºC using dynamic mode. In each extra period were added 10 equivalents more of propargylamine (0.023 g, .041 mmol) to give a total of 30 equivalents in the final solution and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by silica gel chromatography (DCM:MeOH = 10:1 to DCM:MeOH = 7:1) to give **12** (0.087 g, 68%) as a clear wax. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.05 (br, 2H, HC≡CC**H$_2$**), 3.51-3.29 (m, 448H, C**H$_2$**OC**H$_2$**CH$_2$OC**H$_2$**CH$_2$OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.08 (br m, 32H, BocNHC**H$_2$**), 2.17 (br, 1H, **H**C≡CCH$_2$), 1.69-1.60 (m, 120H, OCH$_2$C**H$_2$**CH$_2$), 1.31 (s, 144H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.7 (**C**$_3$N$_3$), 155.9 (**C**O), 81.1 (not found, H**C**≡CCH$_2$), 78.6 (**C**(CH$_3$)$_3$), 70.5 (not found, HC≡**C**CH$_2$), 70.4 (O**C**H$_2$**C**H$_2$O), 70.0 (two lines, O**C**H$_2$**C**H$_2$O), 69.3 (**C**H$_2$CH$_2$CH$_2$O), 69.1 (CH$_2$**C**H$_2$CH$_2$O), 69.0 (CH$_2$CH$_2$**C**H$_2$O), 38.3 (**C**H$_2$CH$_2$CH$_2$O), 37.8 (CH$_2$**C**H$_2$CH$_2$O), 30.1 (not found, HC≡C**C**H$_2$), 29.5 (NH**C**H$_2$CH$_2$CH$_2$O), 28.3 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{428}H_{808}N_{106}O_{122}$ 9386.03, found 9392.20 (M + H)$^+$.

Figure S34. ^{1}H NMR Spectrum of **12.**

Figure S35. ^{13}C NMR Spectrum of **12.**
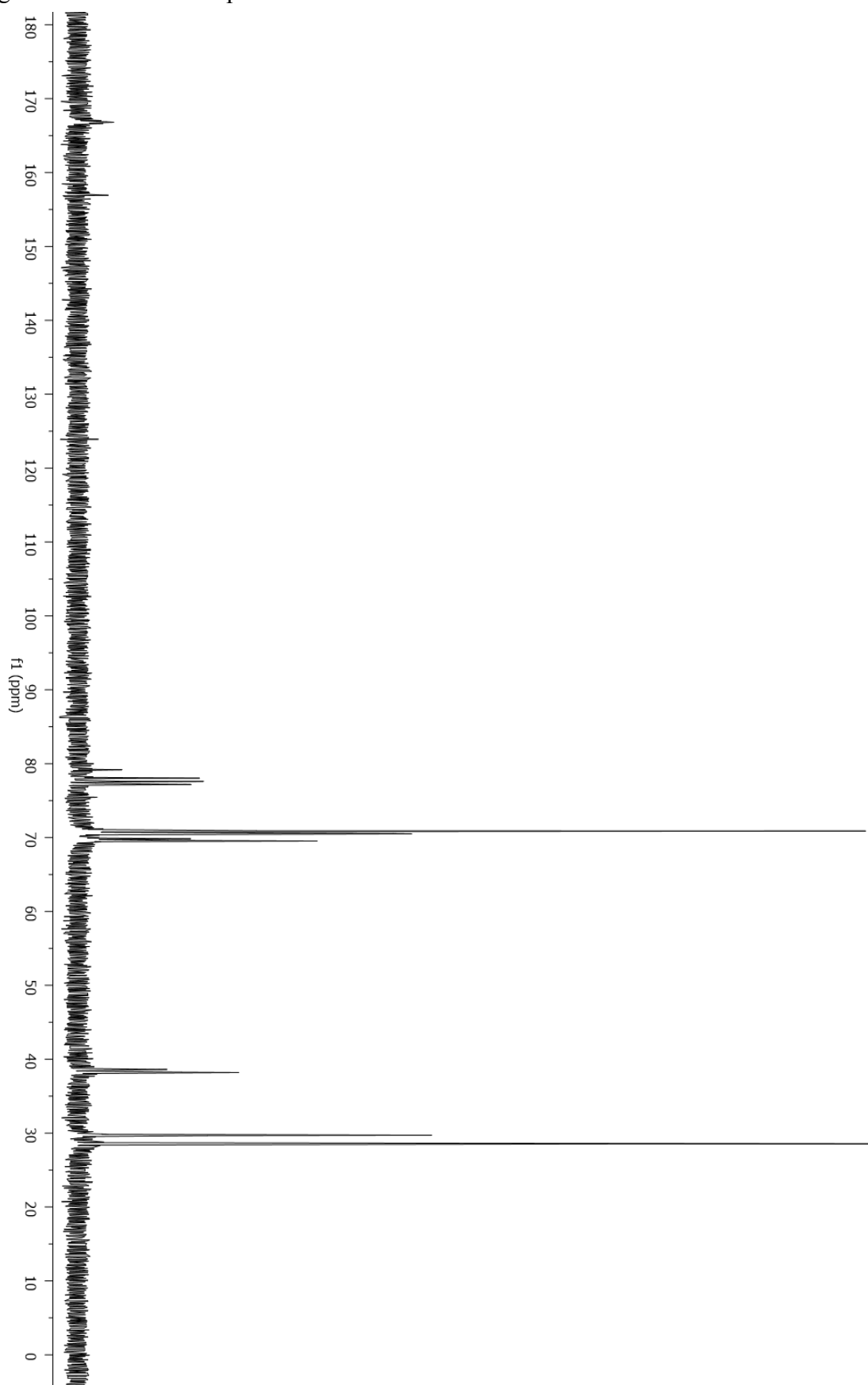
Figure S36. Mass Spectrum of **12.**
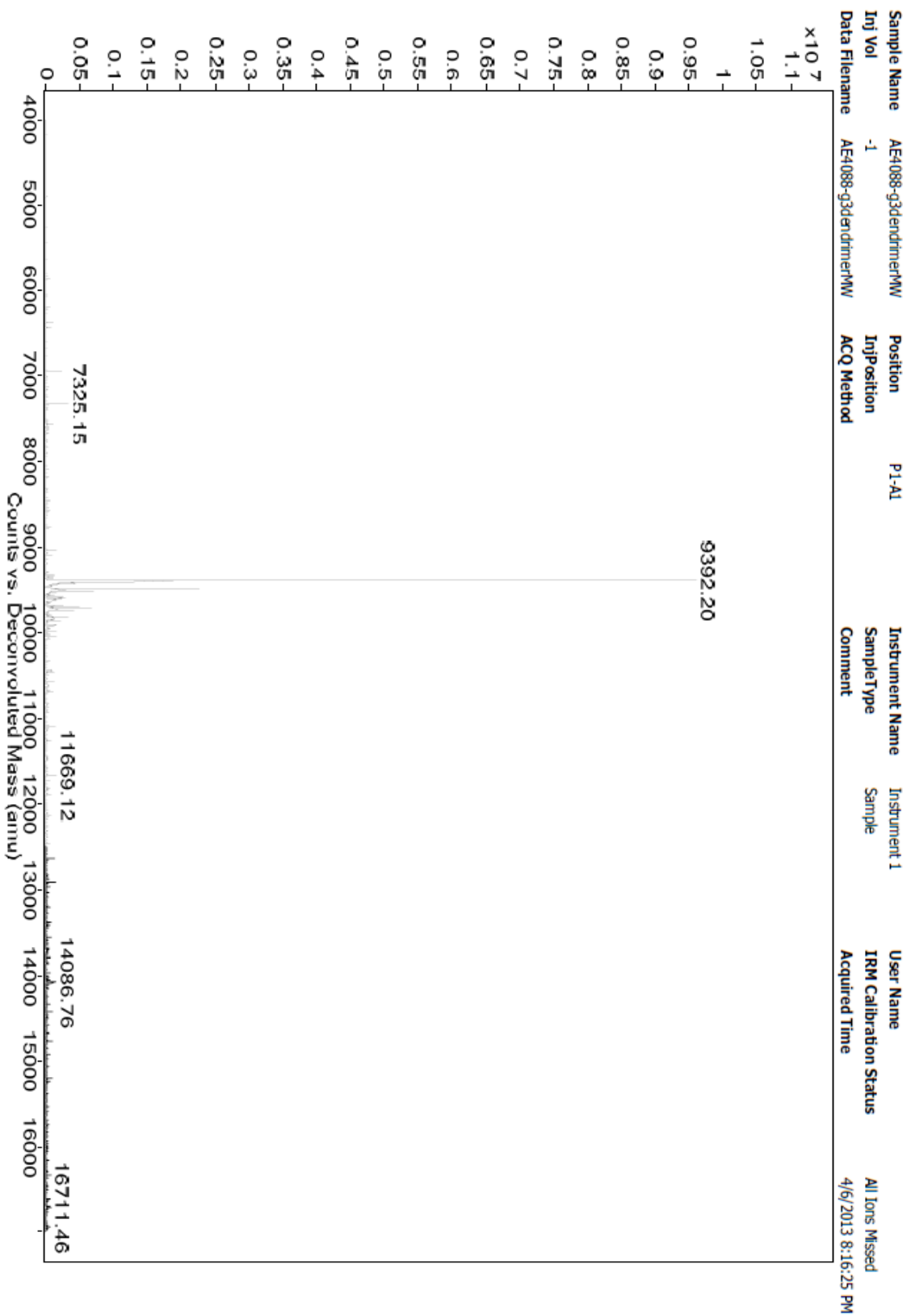
Compound 13. A solution of **12** (0.087 g, 0.009 mmol) in concentrated HCl (0.5 mL) and methanol (1 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for two periods of 3 minutes at 60ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **13** (0.070 g, quantitative) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (br, 2H, HC≡C**CH$_2$**), 3.60-3.38 (m, 448H, **CH$_2$**O**CH$_2$CH$_2$**O**CH$_2$CH$_2$**O**CH$_2$**, C_3N_3-NHC**H$_2$**CH$_2$CH$_2$O), 2.78 (br, 32H, OCH$_2$CH$_2$C**H$_2$**NH$_2$), 2.22 (br, 1H, **H**C≡CCH$_2$), 1.78-1.69 (m, 120H, OCH$_2$C**H$_2$**CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (**C**$_3$N$_3$), 81.1 (not found, HC≡**C**CH$_2$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.5 (HC≡C**C**H$_2$), 70.3 (O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$**C**H$_2$O) 69.5 (**C**H$_2$CH$_2$CH$_2$O), 69.4 (CH$_2$**C**H$_2$CH$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 39.6 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 32.9 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 30.1 (not found, HC≡C**C**H$_2$), 29.7 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{348}H_{680}N_{106}O_{90}$ 7785.19, found 7790.0851 $(M + H)^+$.
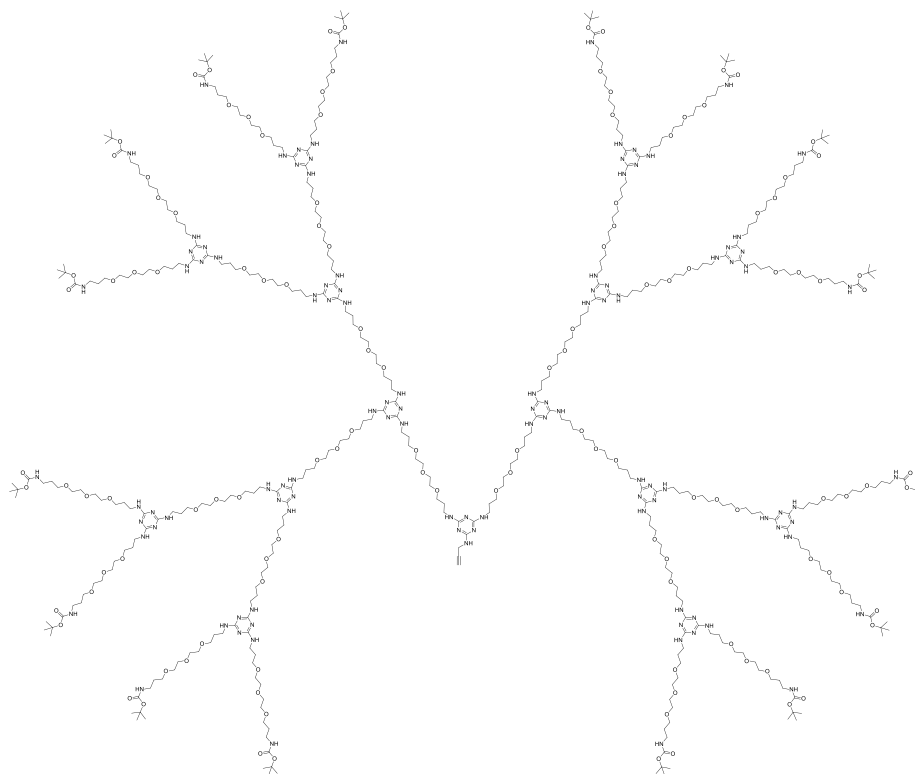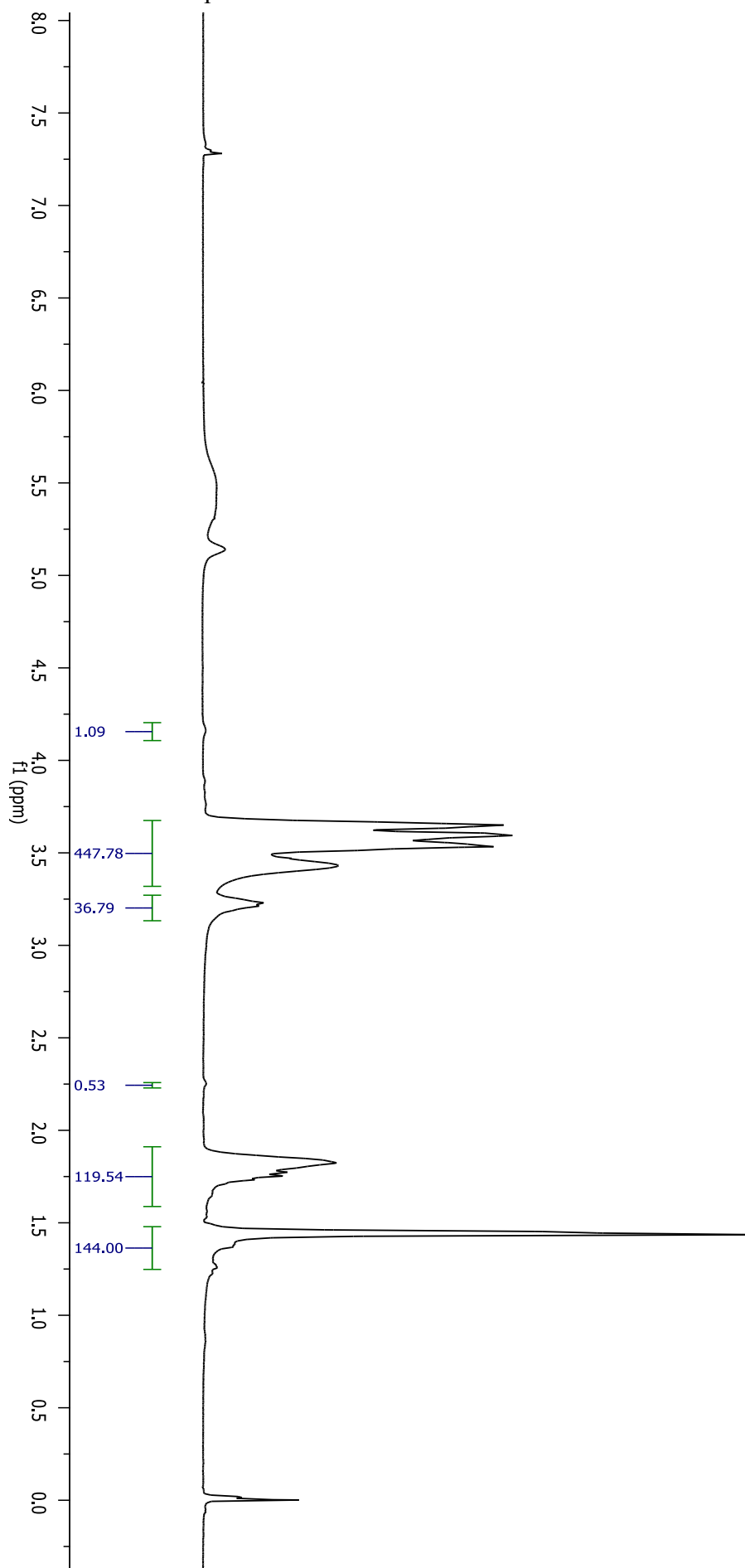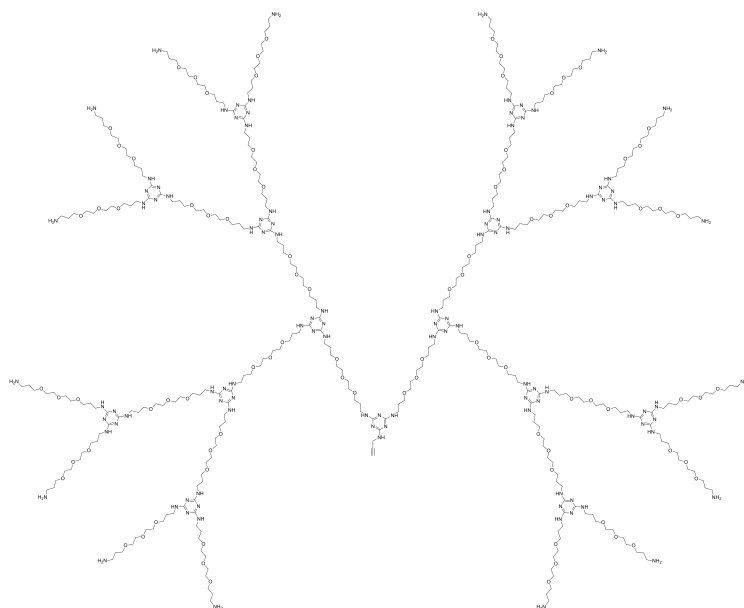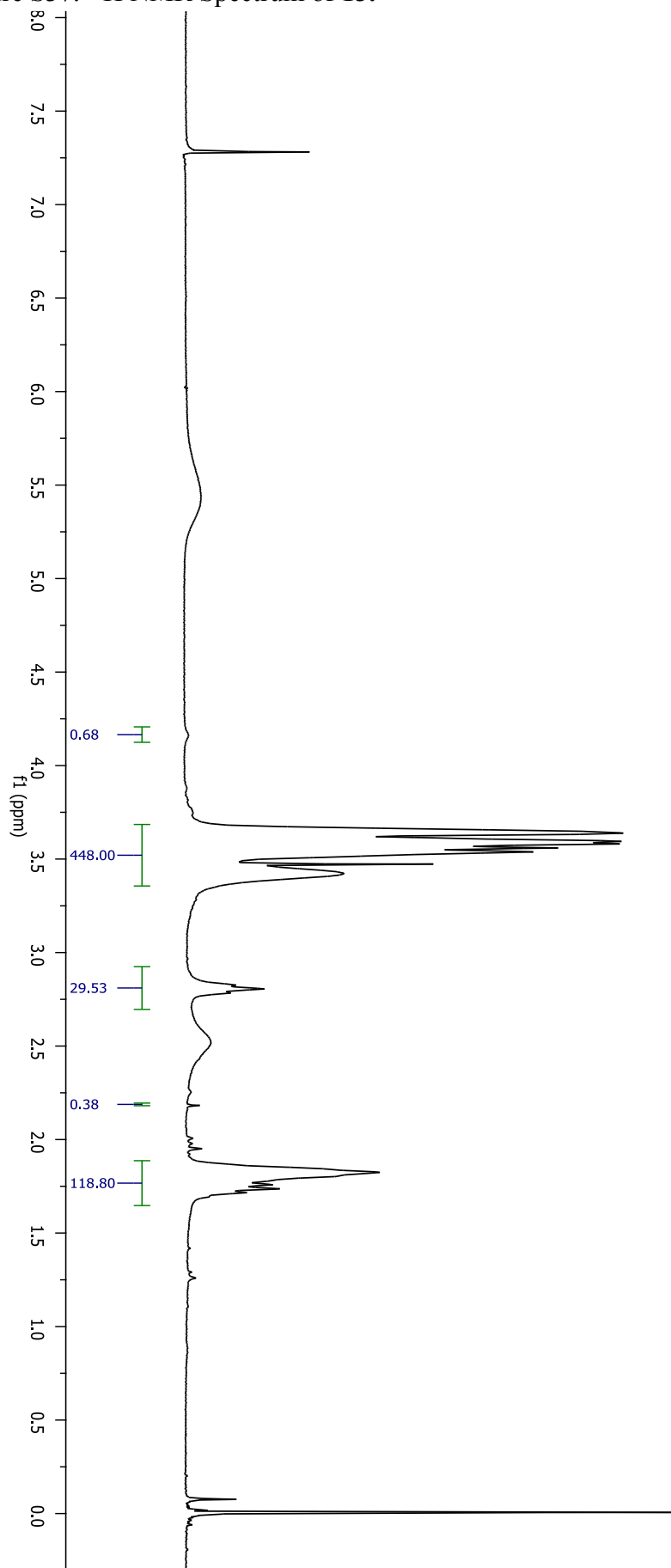
Figure S37. ¹H NMR Spectrum of **13.**

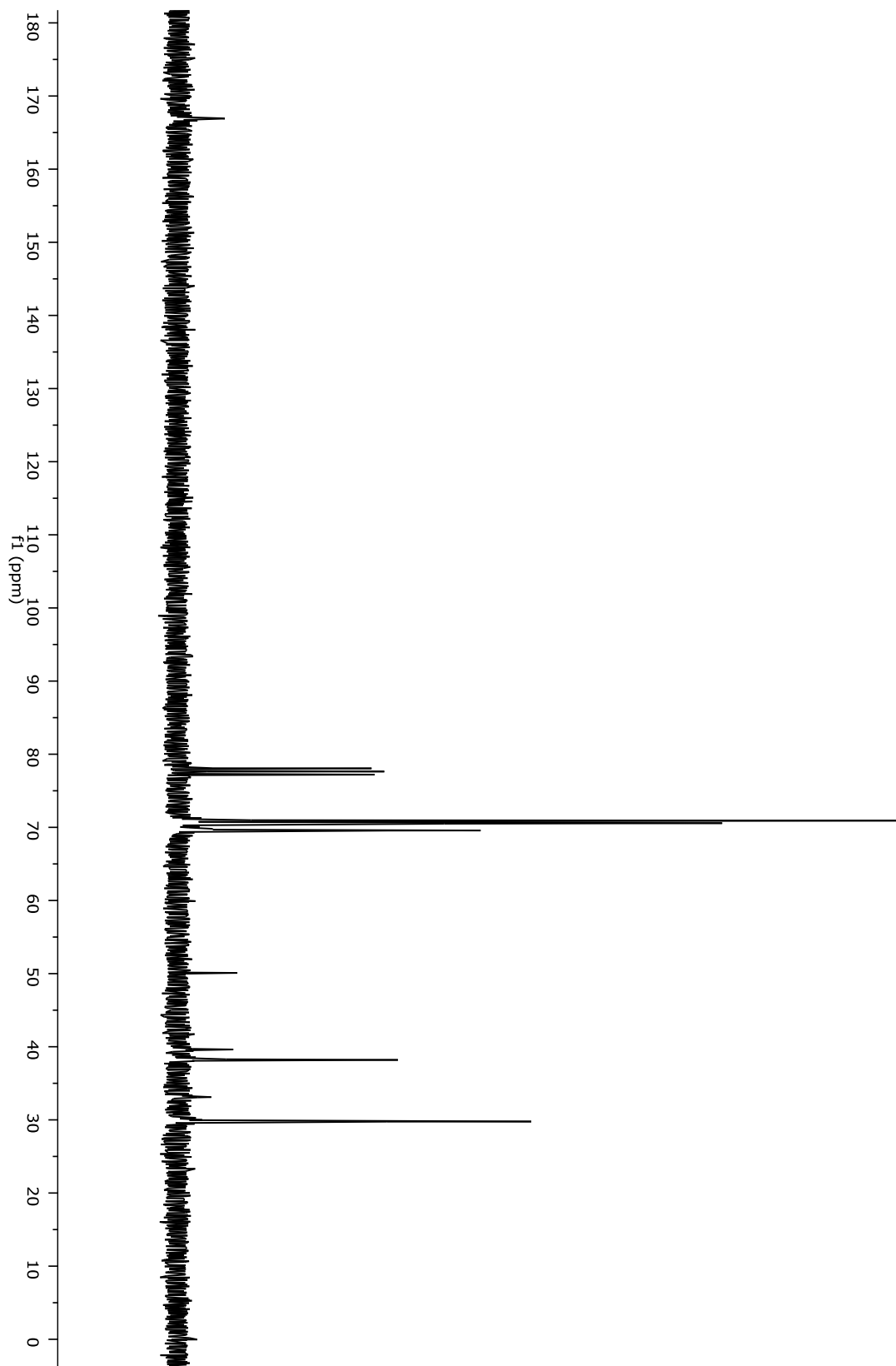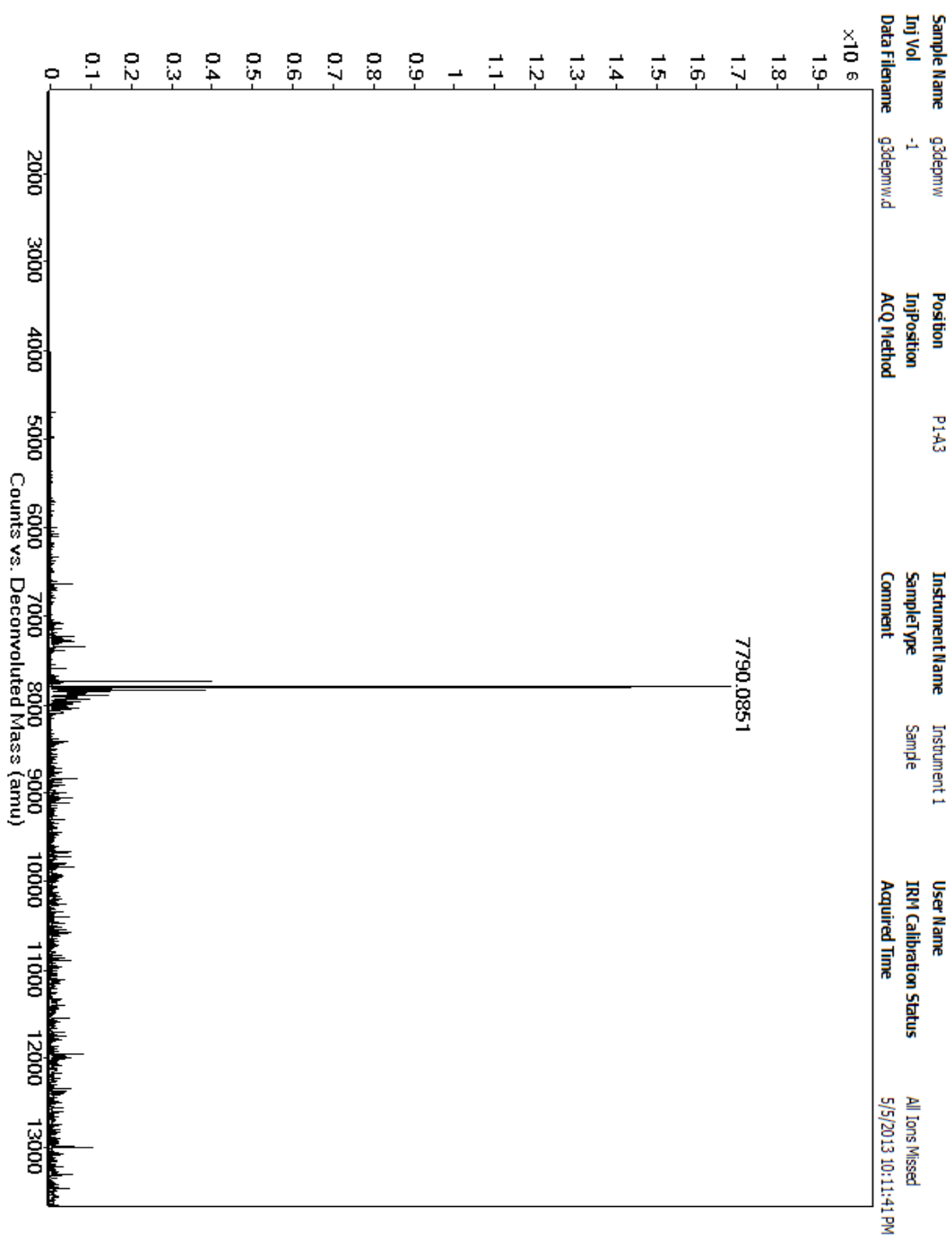Figure S38. ^{13}C NMR Spectrum of **13**.

Figure S39. Mass Spectrum of **13.**

Compound 14. To a mixture of **Compound 3** (150 mg, 0.075 mmol) and 4-(2-azidoethyl)phenol (19 mg, 0.074 mmol) in Terbutanol (TEBOL, 0.8 mL), a solution of $CuSO_4 \cdot 5H_2O$ (4.5 mg, 0.019 mmol) in water (0.3 mL) followed by sodium-L-ascorbate (18 mg, 0.09mmol) was added at room temperature and stirred for 4h. Then, the solution was diluted with dichloromethane (20 mL) and washed three times with 1mM EDTA (20 mL), brine, dried over MgSO4 and concentrated. The crude product was purified by column chromatography (DCM:MeOH = 97:3 → DCM:MeOH = 9:1; to give **14** as a white wax (132 mg, 81 %). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.13 (s, 1H, from triazole), 6.79-6.77 (d, J = 7.2, 2H, HO-C-C**H**=CH-C), 6.72-6.7 (d, J = 8.0, 2H, HO-C-CH=C**H**-C), 4.48-4.47 (t, J = 6.1, 2H, NH-C**H$_2$**-triazole), 3.65-3.43 (m, 88H, **CH$_2$**OC**H$_2$CH$_2$**OC**H$_2$CH$_2$**O**CH$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.21 (br, m, 8H, BocNHC**H$_2$**), 3.04 (m, 2H, triazole-N-C**H$_2$**-CH$_2$-phenol),1.83-1.70 (m, 24H, OCH$_2$C**H$_2$**CH$_2$), 1.44 (s, 36H, C(C**H$_3$**)$_3$); ^{13}C NMR (100 MHz, CDCl3) δ 164.75 (**C$_3$**N$_3$), 164.69 (**C$_3$**N$_3$), 156.05 (**C**O), 145.6 (HO-**C**), 129.9 (CH2**C**=**C**H-CH=CH-C-OH), 127.77 (CH2**C**=CH-CH=CH-C-OH), 122.61 (**C**H from triazole), 115.84 (CH2C=CH-**C**H=**C**H-C-OH), 78.7 (**C**(CH$_3$)$_3$), 70.5 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 51.83 (phenol-CH$_2$**C**H$_2$-Triazole), 38.38 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 35.83 (phenol-**C**H$_2$CH$_2$-Triazole),29.53 (NHCH$_2$**C**H$_2$CH$_2$O), 28.40 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for C$_{100}$H$_{181}$N$_{25}$O$_{27}$ 2164.36, found 2165.66 (M + H)$^+$.
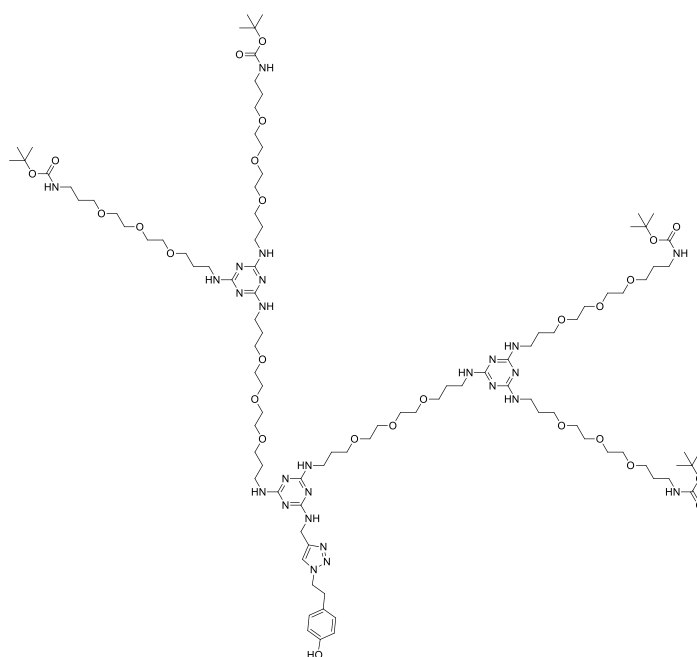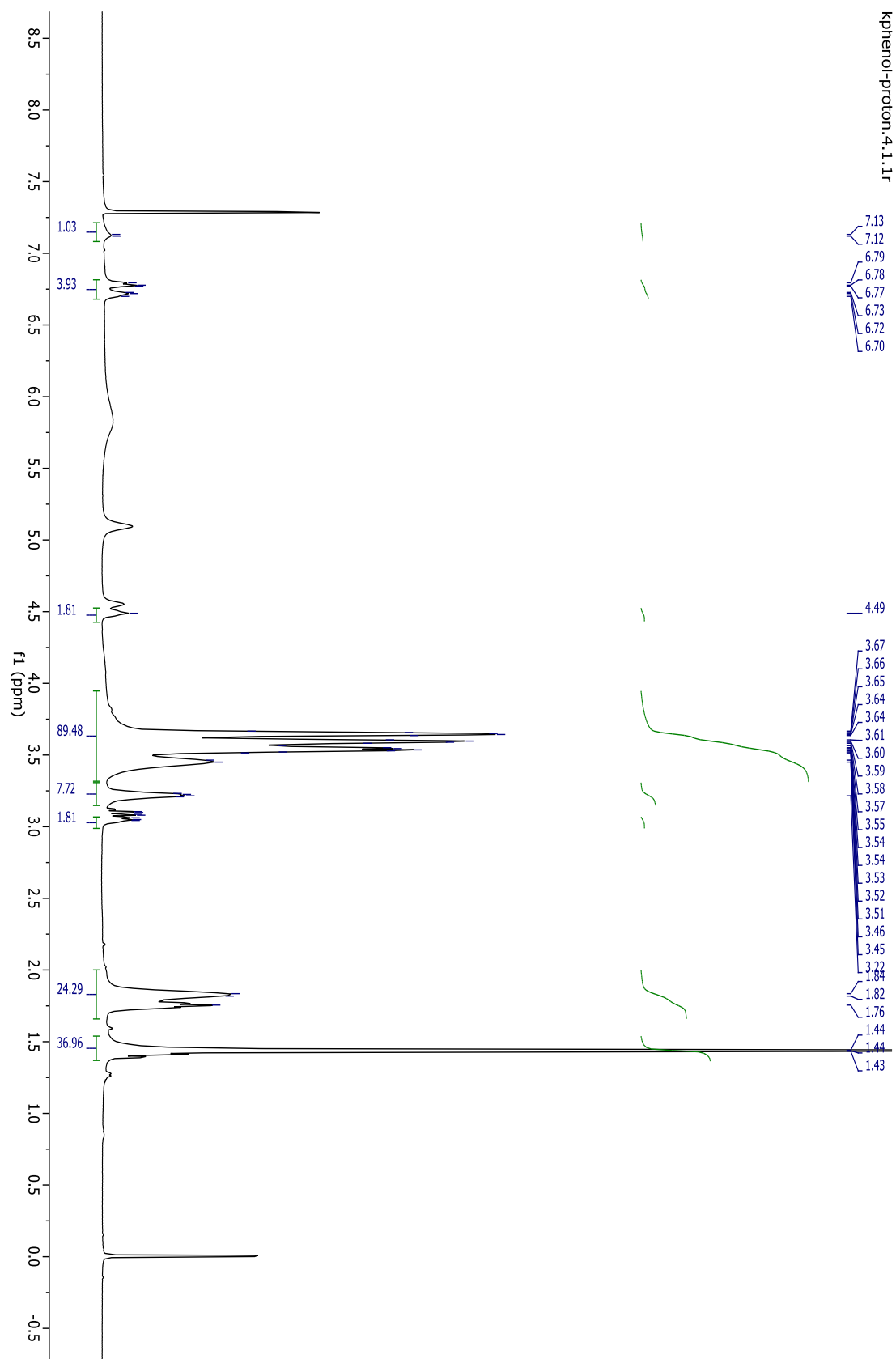
Figure S40. ^{1}H NMR Spectrum of **14.**

Figure S41. ^{13}C NMR Spectrum of **14**.

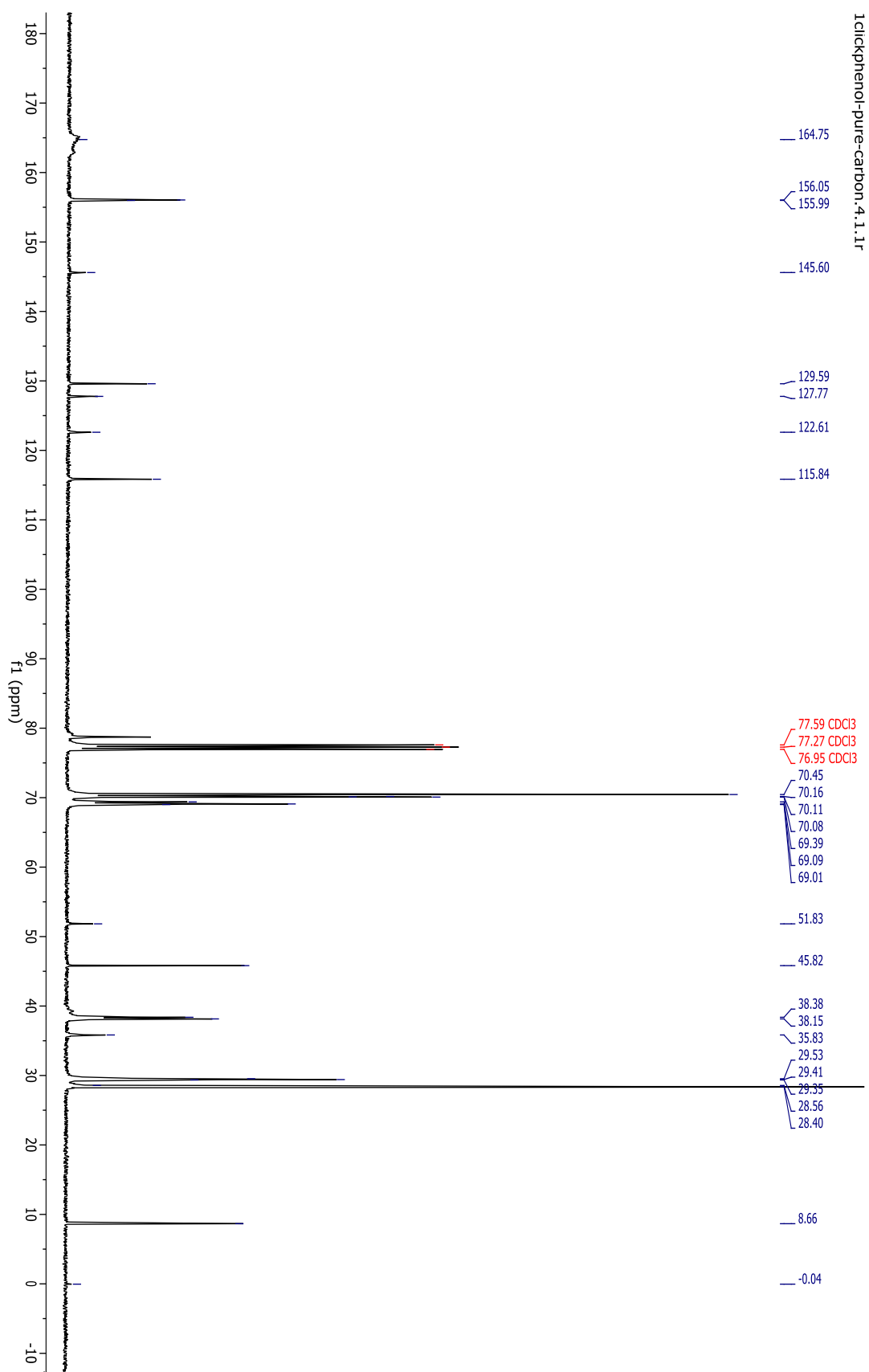Figure S42. Mass Spectrum of **14.**
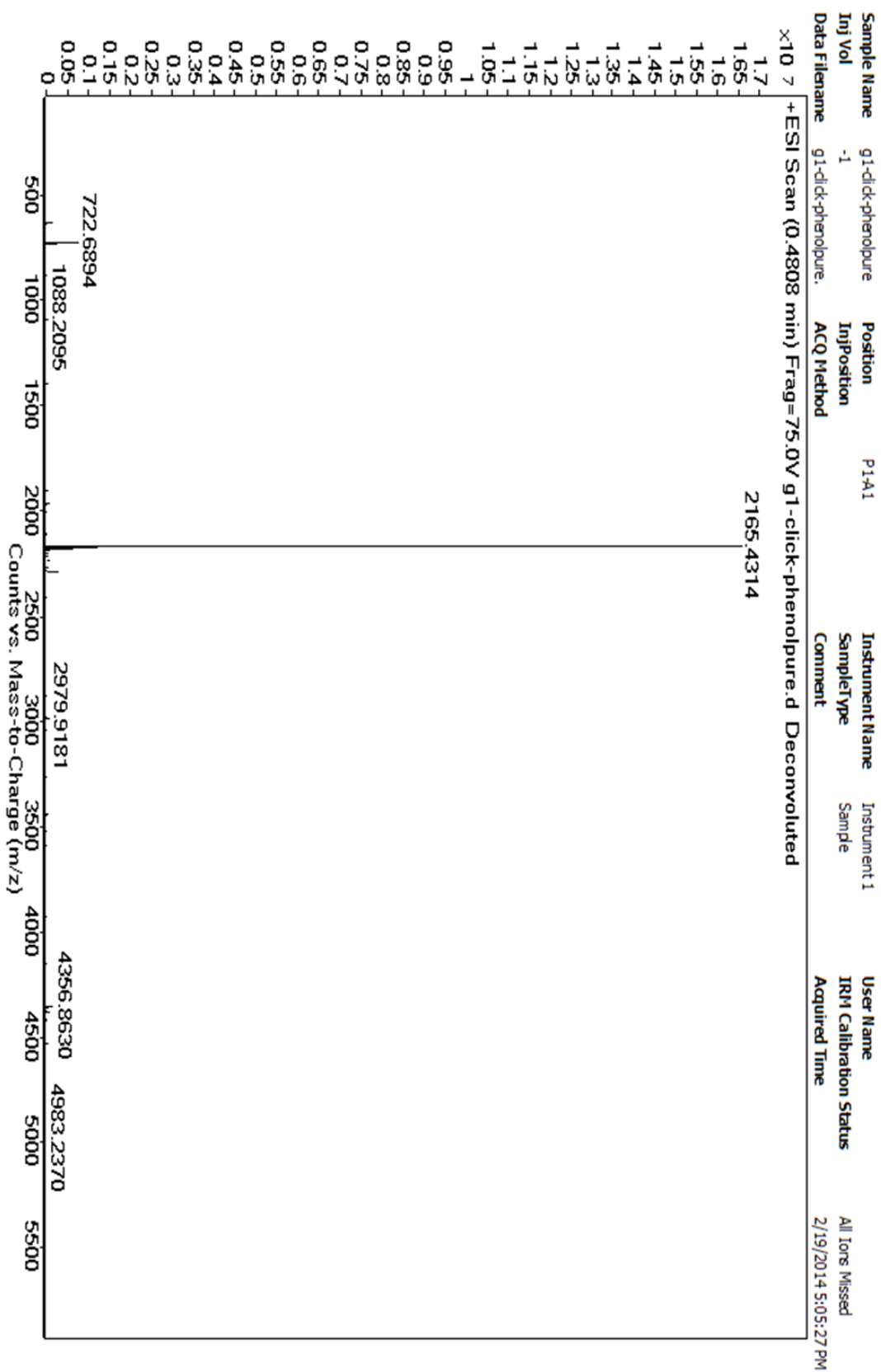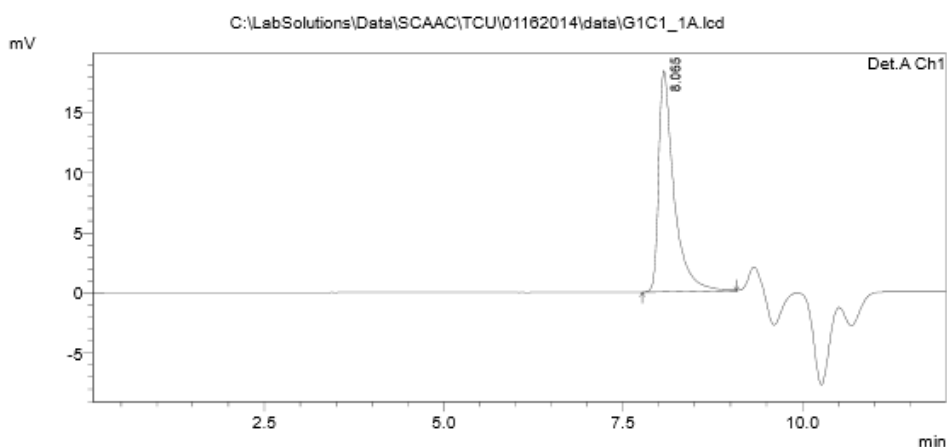
Figure S43. GPC Traces Compound **3**.

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G1C1_1A.lcd

Sample Name   : G1C1
Sample ID   : G1C1
Injection Volume : 50 uL
Data File Name : G1C1_1A.lcd
Data Acquired   : 1/17/2014 5:32:42 PM
Data Processed : 1/21/2014 10:10:14 AM
G1C1 dissolved in THF, concentration is 1mg/mL, Mobile phase is THF running at 1.0 mL/min

<Chromatogram>

1 Det.A Ch1/

GPC Calibration Curve

Method File   : C:\LabSolutions\Data\SCAAC\TCU\01162014\data\calibration1.lcm
Curve Fit Type   : Linear
Function   : f(x)=-1.008573*x+11.53593
    R^2=0.9960443
    Dispersion=0.0292156
Mark-Houwink   : No
Sensitivity Compensation (RID)   : No
IS Correction   : No
GPC Control Sample Correction   : No
Average time for the same M.W   : Yes
Time Conversion   : No
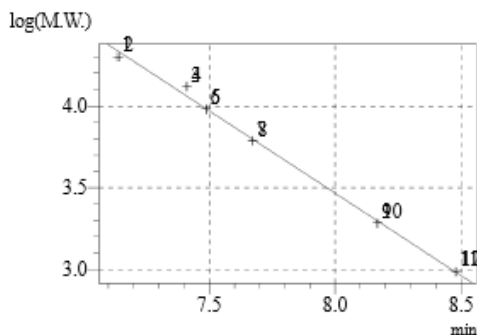
#	Time(min)	Molecular Weight
1	7.135	20000
2	7.142	20000
3	7.411	13200
4	7.412	13200
5	7.486	9580
6	7.486	9580
7	7.670	6140
8	7.674	6140
9	8.167	1920
10	8.168	1920
11	8.477	972
12	8.482	972

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G1C1_1A.lcd

GPC Graph
G1C1 C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G1C1_1A.lcd
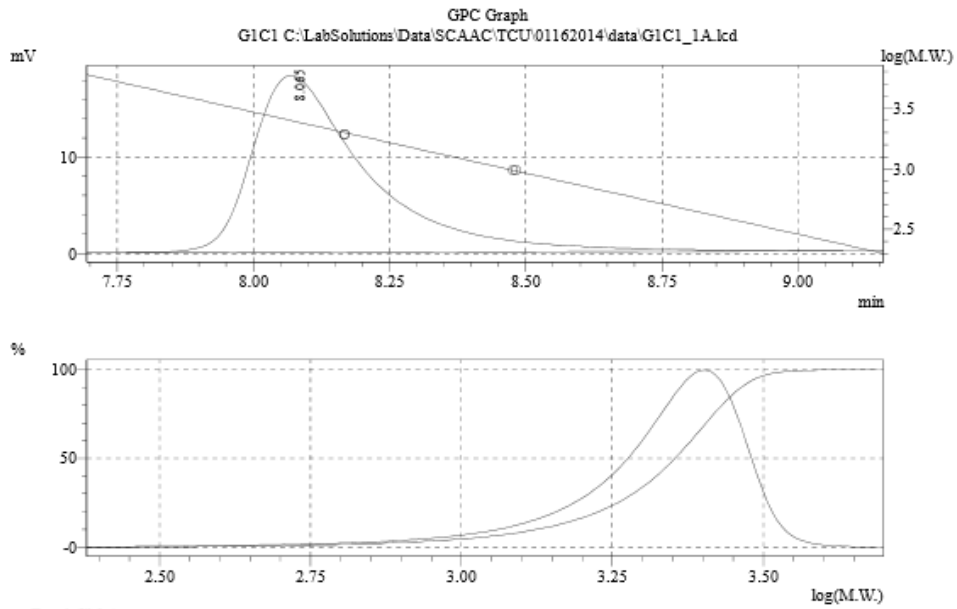
Det.A Ch1 /

GPC Summary

Chromatogram Det.A Ch1

#	Title	Mn	Mw	Mz	Mz1	Mv	Mw/Mn	Mz/Mw
1	G1C1_1A.lcd	1941	2206	2380	2508	0	1.13665	1.07870
	Average	1941	2206	2380	2508	0	1.13665	1.07870
	%RSD	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Maximum	1941	2206	2380	2508	0	1.13665	1.07870
	Minimum	1941	2206	2380	2508	0	1.13665	1.07870
	SD	0	0	0	0	0	0.00000	0.00000

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G1C1_1A.lcd

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Figure S44. GPC Traces of Compound **5**.

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G2C1_1A.lcd

Sample Name   : G2C1
Sample ID   : G2C1
Injection Volume : 50 uL
Data File Name   : G2C1_1A.lcd
Data Acquired   : 1/17/2014 5:57:40 PM
Data Processed   : 1/21/2014 10:12:20 AM
G2C1 dissolved in THF, concentration is 1mg/mL, Mobile phase is THF running at 1.0 mL/min
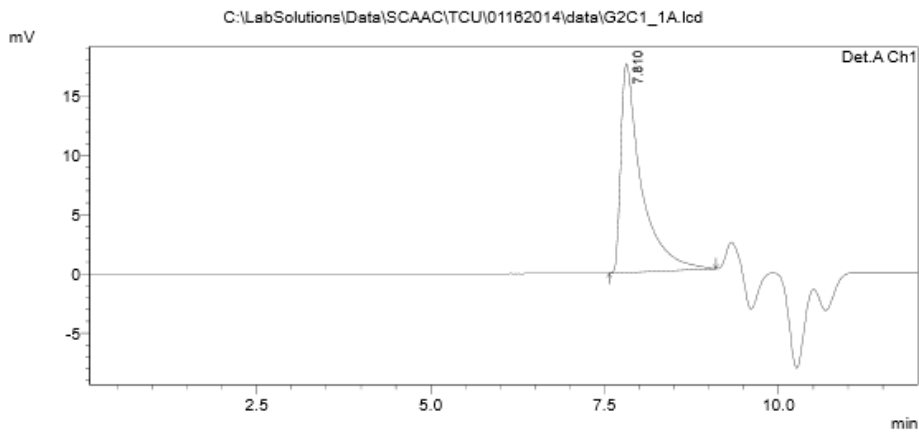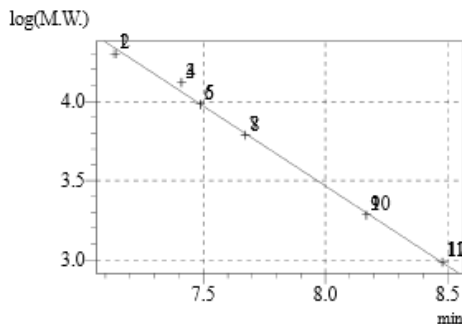
<Chromatogram>

1 Det.A Ch1/

GPC Calibration Curve

Method File   : C:\LabSolutions\Data\SCAAC\TCU\01162014\data\calibrationl.lcm
Curve Fit Type   : Linear
Function   : f(x)=-1.008573*x+11.53593
    R^2=0.9960443
    Dispersion=0.0292156
Mark-Houwink   : No
Sensitivity Compensation (RID)   : No
IS Correction   : No
GPC Control Sample Correction   : No
Average time for the same M.W   : Yes
Time Conversion   : No

#	Time(min)	Molecular Weight
1	7.135	20000
2	7.142	20000
3	7.411	13200
4	7.412	13200
5	7.486	9580
6	7.486	9580
7	7.670	6140
8	7.674	6140
9	8.167	1920
10	8.168	1920
11	8.477	972
12	8.482	972

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G2C1_1A.lcd

GPC Graph
G2C1 C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G2C1_1A.lcd
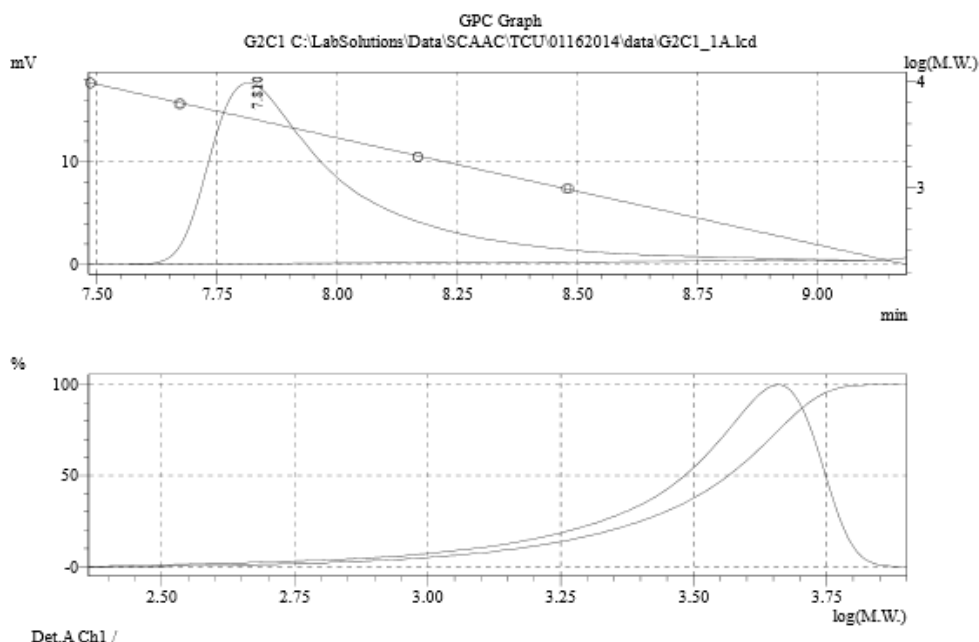
Det.A Ch1 /

GPC Summary

Chromatogram Det.A Ch1

#	Title	Mn	Mw	Mz	Mz1	Mv	Mw/Mn	Mz/Mw
1	G2C1_1A.lcd	2606	3546	4096	4442	0	1.36056	1.15519
	Average	2606	3546	4096	4442	0	1.36056	1.15519
	%RSD	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Maximum	2606	3546	4096	4442	0	1.36056	1.15519
	Minimum	2606	3546	4096	4442	0	1.36056	1.15519
	SD	0	0	0	0	0	0.00000	0.00000

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G2C1_1A.lcd

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Figure S45. GPC Traces of Compound **7**.

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G3C1_1A.lcd

Sample Name : G3C1
Sample ID : G3C1
Injection Volume : 50 uL
Data File Name : G3C1_1A.lcd
Data Acquired : 1/17/2014 6:22:37 PM
Data Processed : 1/17/2014 11:29:12 PM
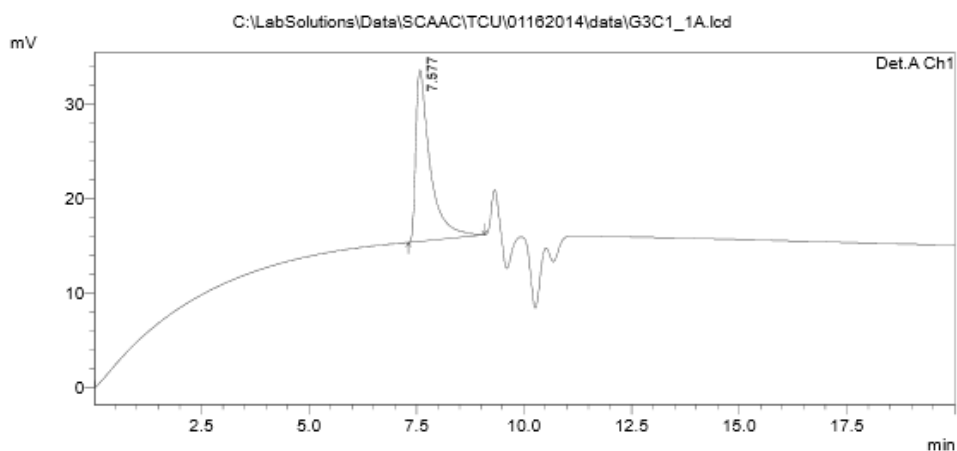G3C1 dissolved in THF, concentration is 1mg/mL, Mobile phase is THF running at 1.0 mL/min

<Chromatogram>

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G3C1_1A.lcd

1 Det.A Ch1/

GPC Calibration Curve

Method File : C:\LabSolutions\Data\SCAAC\TCU\01162014\data\calibrationl.lcm
Curve Fit Type : Linear
Function : f(x)=-1.008573*x+11.53593
 R^2=0.9960443
 Dispersion=0.0292156
Mark-Houwink : No
Sensitivity Compensation (RID) : No
IS Correction : No
GPC Control Sample Correction : No
Average time for the same M.W : Yes
Time Conversion : No
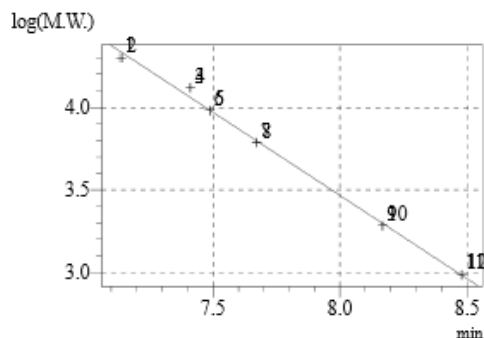
#	Time(min)	Molecular Weight
1	7.135	20000
2	7.142	20000
3	7.411	13200
4	7.412	13200
5	7.486	9580
6	7.486	9580
7	7.670	6140
8	7.674	6140
9	8.167	1920
10	8.168	1920
11	8.477	972
12	8.482	972

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G3C1_1A.lcd

GPC Graph
G3C1 C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G3C1_1A.lcd
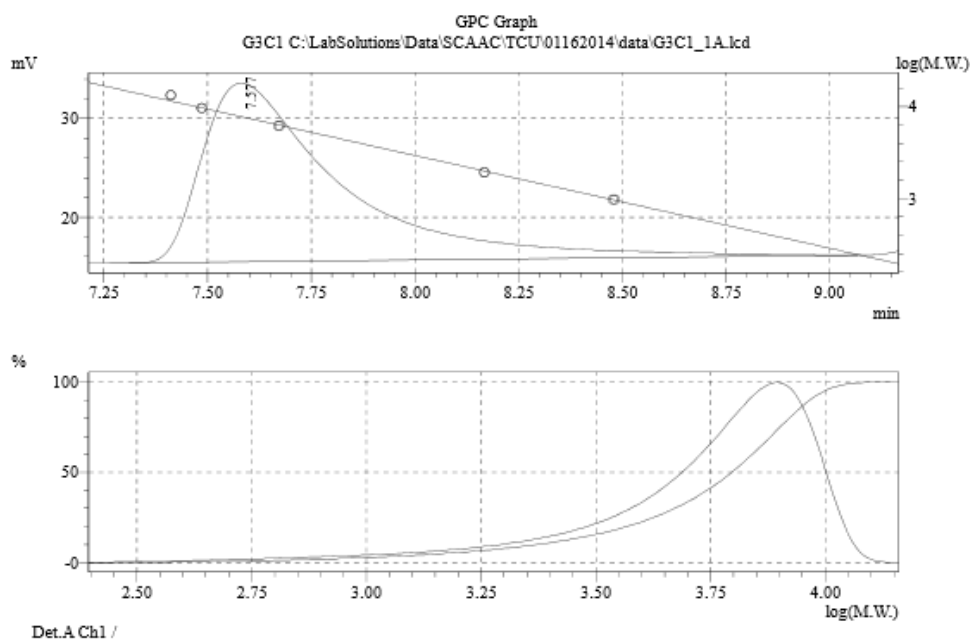
Det.A Ch1 /

GPC Summary

Chromatogram Det.A Ch1

#	Title	Mn	Mw	Mz	Mz1	Mv	Mw/Mn	Mz/Mw
1	G3C1_1A.lcd	4127	6096	7178	7854	0	1.47700	1.17756
	Average	4127	6096	7178	7854	0	1.47700	1.17756
	%RSD	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Maximum	4127	6096	7178	7854	0	1.47700	1.17756
	Minimum	4127	6096	7178	7854	0	1.47700	1.17756
	SD	0	0	0	0	0	0.00000	0.00000

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\G3C1_1A.lcd

Figure S45. GPC-THF Blank Injection.

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\SCAAC\TCU\01162014\data\thf4.lcd

Sample Name   : thf
Sample ID   : thf
Injection Volume   : 50 uL
Data File Name   : thf4.lcd
Data Acquired   : 1/21/2014 1:24:05 PM
Data Processed   : 1/21/2014 1:44:07 PM
thf blank; Mobile phase is THF running at 1.0 mL/min
using Agelient PLgel Mixed C column (8.0x300mm, 5uM) no guard

<Chromatogram>

1 Det.A Ch1/